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Healthcare is an enormously complex part of the global economy. It consists of multiple stakeholders, many distinct industries, highly sophisticated technologies, and critical products and services that affect the lives of virtually everyone in the world. To fully appreciate the complexity of this field, consider the pharmaceutical or drug you took this morning for allergies or the medical device you used while exercising to measure your heart rate. How did those products come about?

Most likely, the process began decades ago, with scientists in academia making discoveries about biology and the specific mechanisms of a given disease or condition. These discoveries were then used by a different set of scientists and clinicians—most likely in a biotechnology company—to develop potential methods for disrupting those mechanisms, typically using chemical or biological agents. These agents were first tested in animals such as mice, dogs, and primates, and if the results showed promise, they progressed to human clinical trials. Because of the potential for toxic side effects, when clinical trials go wrong, people can die. Therefore, the highly methodical process by which clinical trials are designed and conducted requires extraordinary skill, patience, and regulatory oversight by government agencies such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA). From start to finish, this process can take a decade or longer, and biotechnology companies will often partner with or be acquired by larger pharmaceutical companies to complete the trials. And at the end of this lengthy process, there’s no guarantee that the drug or device candidate will turn out to be safe and effective. In fact, historically, the overall probability of success of clinical trials is about 8%, which translates to a failure rate of about 92%.

In the unlikely event that clinical trials do show safety and effectiveness, the company sponsoring the trial can submit an application to the FDA for a license to produce,
After a detailed review of the company’s manufacturing processes, marketing and distribution practices, and patient safety measures, regulators will decide whether to award such a license. If a license is granted, the company can introduce the therapeutic into the healthcare delivery system, which involves an entirely different set of stakeholders that includes pharmaceutical sales representatives, doctors, hospitals, academic medical centers, public and private health insurance companies, pharmacies, pharmacy benefit managers, and patients. It’s through this administrative labyrinth that an approved drug or device finally reaches you, the patient. This complex process (see Figure 1.1), including the role that money and financing plays, is the main focus of this text.

1.1 FINANCING: THE LIFEBLOOD OF BIOMEDICAL INNOVATION

Despite the many different parties and processes involved in drug development and delivery, there’s one common denominator: the need for financing. Financing is needed to cover the cost of laboratory equipment, space, and supplies, patient volunteers, the salaries of scientists, engineers, and clinicians, and filing fees for regulatory approval, and the cost of manufacturing, marketing, distributing, and monitoring the approved drug. Because financial capital is the lifeblood of this entire value chain from the laboratory to the patient, issues such as business models, investor behavior, risk and reward trade-offs, and other financial considerations play a critical role in biomedical innovation.

In some instances, financial considerations dominate decision making and end up driving the scientific and medical agendas of biotechnology and pharmaceutical
(biopharma) companies. In one sense, this shouldn’t be too surprising. The process of developing a new drug or medical device typically requires hundreds of millions of dollars paid out over a decade or more, with a probability of success that’s often less than 10%. With these challenges, it’s no surprise that financing opportunities and constraints can drive the priorities of the biopharma industry.

We believe this state of affairs is backward. Shouldn’t the science be driving the financing decisions?

In a surprising number of cases, however, we’ve found that biopharma decision makers aren’t familiar with the basic principles of financial analysis. As a result, these decision makers sometimes delegate important financial decisions to others who may not have an appreciation of the time frames and risk of biomedical research and development (R&D). The decision makers are then shocked when their work is interrupted because their funding has run out at the worst possible moment in their scientific and clinical agendas. If this happens at a time when raising additional capital is difficult, if not impossible (e.g., during an economic recession), years of hard work and millions of dollars of valuable research—research that could have helped many desperate patients—may be abandoned and, ultimately, destroyed.

Our goal in writing this textbook is to help remedy this situation by providing life scientists and clinicians, biotechnology entrepreneurs, pharmaceutical company executives, regulators, patients, philanthropists, and other stakeholders of the vast biomedical ecosystem with the key financial principles and tools most relevant to the biopharma industry. The tools we cover include discounted cash flow analysis, portfolio theory, real options analysis, decision trees, Monte Carlo simulation, securitization, and other techniques broadly known among investment professionals as financial engineering. If these terms are unfamiliar to you, good! You’re the reason we wrote this book. Better financing and business decisions can lower the cost of capital for drug development, increase the amount of funding devoted to biomedicine, and get new and better therapies to patients faster.

One caveat about what this textbook does not cover: the economics of healthcare delivery. Because there are already several excellent textbooks on hospital administration, health insurance coverage, healthcare policy, and cost–benefit analysis and other health technology assessment tools, there’s no need for us to cover these topics here. Instead, our focus is on how new drugs, devices, diagnostics, and other healthcare innovations get financed from start to finish and what can be done from the financial engineering perspective to make this process more efficient.

Our motivation isn’t just academic. Both of us have had close friends and family members affected by cancer and other illnesses. As financial engineers, we felt powerless to help them in any meaningful way. Ironically, our line of work regularly exposes us to the many scientific and medical breakthroughs that seem to be occurring almost

---

2Traditionally, biotechnology referred to medicines derived from living organisms, such as enzymes for enzyme replacement therapy, and pharmaceuticals related to medicines that were chemically synthesized. However, it has become common for companies to use both biological and chemical sources in their R&D efforts (hence the coinage of the term biopharma), and so the distinction we make is based on a company’s size and stage in its life cycle.
daily. By helping you—a member of the healthcare ecosystem—learn how to effectively harness financial tools to fund these biomedical innovations, we believe that together we can make a difference in patients’ lives. There’s no better time to be investing in the future of our health than now.

1.2 BEING HARVEY LODISH

The potential impact of such investments became apparent to us through the remarkable story of Harvey Lodish, a world-renowned cellular biologist at the Whitehead Institute for Biomedical Research at MIT.

In 1983, Dr. Lodish was approached by a biotech venture capitalist to join an effort to develop a new treatment for Gaucher disease, a rare inherited disorder that causes a deficiency in an important “housekeeping” enzyme. When this enzyme is absent or nonfunctional, microscopic fat droplets build up in white blood cells, the liver, the spleen, and bone marrow. As a result, the size of the liver and spleen increase dramatically; blood cells are destroyed prematurely, leading to anemia and a tendency to bruise easily; and the structure of bone tissue is disrupted, leading to severe joint pain and osteoporosis. For a subset of Gaucher patients, this disease is usually terminal by the time they reach their late teens, and in 1983 no treatments were available.

Thanks to Dr. Lodish and other scientists working with him at a biotech start-up, an effective drug was developed—the first enzyme replacement therapy to reach patients—and in 1991, the FDA approved the new treatment, Ceredase (algglucerase). This drug, and its subsequent improvements, has turned this deadly disease into a chronic but medically manageable condition. Their little start-up, Genzyme, eventually grew into a highly successful company that was acquired in 2011 by the French pharmaceutical company Sanofi for a little more than $20 billion.

But the most remarkable part of this story occurred in 2002. In that year, Dr. Lodish’s daughter became pregnant with her second child and discovered via prenatal screening that her son had the mutation for Gaucher disease. Ten years later, when the child began showing the symptoms of the disease, he was treated with the drug his grandfather had helped develop decades before he was born. Thanks to this drug, Dr. Lodish’s

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3One of the most puzzling things about the pharmaceutical industry is that drugs always seem to have two names, one capitalized (known as “brand” names) and the other lowercase (known as “generic” names). Why? The lowercase name is assigned according to a standardized nonproprietary scientific naming convention that identifies the drug type, so that the same drug has the same name everywhere. For example, the cancer drug imatinib refers to the specific chemical compound C29H31N7O regardless of what hospital or country you’re in, and the suffix “-inib” indicates that it’s an angiogenesis inhibitor, meaning that it works by slowing or stopping the growth of blood vessels in cancerous tumors. Two organizations are responsible for assigning these names that communicate the specific medical properties of the drug: the United States Adopted Names (USAN) Council and the World Health Organization (WHO) International Nonproprietary Names (INN) Programme. The drug’s capitalized name is assigned by the biopharma company that owns and develops the compound, and this name is chosen primarily with branding and marketing considerations in mind. The brand name for imatinib is Gleevec, which is trademarked by and proprietary to its owner, the pharmaceutical company Novartis. In this text, we’ll follow the convention of providing both names when a drug is first cited, after which we’ll use only the brand name.
grandson as well as tens of thousands of other Gaucher patients now live completely normal lives.

What an extraordinary twist of fate. When he undertook this project to treat Gaucher disease, Dr. Lodish had no idea he would be participating in something that would one day save the life of his as-yet-unborn grandson. We would all love to be Harvey Lodish, but for most of us without a biomedical background, this is an impossibility. However, it became clear to us after studying the business of biomedicine that we can all be Harvey Lodish if we help finance the therapies that could one day save the lives of our future grandchildren.

1.3 CONVERGENCE

Another reason for studying healthcare finance is the growing need for financing due to the unprecedented pace of discovery and innovation that biomedicine is currently experiencing, something that MIT scientists Phillip Sharp, Tyler Jacks, and Susan Hockfield (2016) call “convergence.” Over the last two decades, a convergence of knowledge in the life sciences, the physical sciences, and engineering has brought biomedicine—and, consequently, human evolution—to an inflection point. A significant milestone in the process of convergence was reached in 1998, during the first clinical trial of the drug Gleevec (imatinib), a chemical compound used to treat chronic myelogenous leukemia, a specific type of blood cancer. Gleevec was discovered by a team led by Dr. Nicholas Lydon, a biochemist working at the pharmaceutical company Ciba-Geigy (now Novartis), and the oncologist Dr. Brian Druker of the Oregon Health & Science University.

The team developed Gleevec using rational drug design, the process of engineering new treatments based on specific knowledge of a biological target such as a protein. As part of their research, the scientists used high-throughput screening, an automated process involving a combination of specialized machines, computational algorithms, and biochemistry that allows researchers to quickly conduct millions of biochemical tests. Through this process, the team was able to identify a compound that could selectively inhibit the hyperactive Bcr-Abl tyrosine kinase protein, which had been implicated in the biological development, or pathogenesis, of the cancer. This process illustrates what we mean by convergence.

In 1998, the team began clinical trials to test the effectiveness and safety of the drug in humans. Of the 31 patients treated, all 31 experienced complete remission of the disease. As a result of this astonishing outcome, the FDA approved the drug only 3 years later in 2001, the fastest time to approval by the FDA of any drug up to that point. Since then, Gleevec has saved the lives of thousands of leukemia patients each year and has also generated tremendous revenues for Novartis: In 2015, Novartis reported $4.7 billion in annual sales just from this one drug. Figure 1.2 summarizes Gleevec’s development time line.

\(^4\)See footnote 3.
The rate at which breakthroughs such as Gleevec are being made is accelerating. In 2004, the anti-cancer drug Avastin (bevacizumab), also developed using rational drug design, was approved. In 2008, Sutent (sunitinib) was approved for the treatment of two cancers: renal cell carcinoma and gastrointestinal stromal tumors. In fact, since the success of the Gleevec model, more than 50 new drugs created via rational drug design have been approved.

More recently, an entirely new set of treatments called immunotherapies, treatments that use the body’s own immune system to fight cancer, has emerged. For example, in 2014, Keytruda (pembrolizumab) was approved to treat the deadly form of skin cancer known as melanoma. This drug received national attention in 2015 when it was used to treat former president Jimmy Carter’s Stage IV metastatic melanoma (which had spread to his liver and brain) and apparently cured him.

At the same time that biomedicine has reached an inflection point, however, funding innovation remains a challenge that’s becoming more complex. This is particularly true during the initial stages of therapeutic development (preclinical development; i.e., before a therapeutic is ready for human clinical trials) as well as during the subsequent stage when therapeutics are first tested in human subjects (early-stage clinical development). But how can funding be a challenge when a single drug like Gleevec can generate $4.7 billion in just one year?
1.4 BIOMEDICINE FROM A FINANCIAL PERSPECTIVE

Before delving into the financial challenges facing the biopharma industry, we should clarify some terms we’ll be using throughout this text and agree on certain conventions. The term drug typically refers to a chemical or biological agent that’s administered to a patient, but there are other broad classes of therapeutics that are part of the biopharma industry. These include medical devices (e.g., magnetic resonance imaging equipment, dialysis machines, artificial hearts), diagnostics (e.g., blood tests, cancer diagnostics, genetic sequencing), and bioinformatics (e.g., computational analysis of genetic profiles and their associations with specific diseases, mathematical and numerical simulations of the properties of chemical and biological compounds, and machine-learning predictions of drug efficacy, toxicity, and clinical trial outcomes). For most of this textbook, the financial methods and tools covered are so broadly applicable to all of these industry segments that we’ll use the more compact phrase drug development as shorthand to mean “drug, device, diagnostics, and bioinformatics development.” In some cases, we’ll use the more generic term, therapeutic, to mean any treatment or study that can benefit a patient with a given illness. In other cases, when we refer to a specific class of therapeutic such as devices or diagnostics, it should be clear from the context whether the term is being used in the specific or broader sense.

The drug development industry can be divided roughly into two components: large pharmaceutical companies (sometimes called big pharma) like Johnson & Johnson, Merck, Novartis, Pfizer, and Roche, and smaller biotechnology companies, often founded by scientist-entrepreneurs, that bring the very newest ideas from the laboratory into the clinic.

A typical big pharma company has multiple approved drugs in the market that treat many different diseases and many more drug candidates under development in its pipeline, has billions of dollars in annual sales, employs many thousands of professionals all over the world, and is profitable (meaning its annual revenues exceed its annual costs, hence it has positive annual earnings). In contrast, a typical biotech company is much smaller in every dimension and usually has no approved drugs and no revenues. Biotech companies are often said to be burning cash. As odd as it may seem, in some cases, the greater the biotech’s cash burn rate (the dollars spent per month), the greater its value, because more cash spent often (but not always) implies more progress. Biotech companies are focused on conducting scientific and clinical investigations to develop a specific therapeutic that may eventually become an approved drug or device.

In recent years, a third category of companies known as small pharma or specialty pharma has emerged. These are much larger than the typical biotech start-up but may be generating revenues and even profits, usually with only one or two approved drugs in a relatively narrow therapeutic area (like Gaucher disease).

Figure 1.3 illustrates the performance of the U.S. biotech and pharma stock market indexes from December 5, 1994, to May 12, 2021. Their performance is plotted on a logarithmic scale on the vertical axis, so that equal vertical distances represent equal rates of return. The slope of each line therefore tells us how quickly each index is growing.
CHAPTER 1

Pharmaceutical companies grew at a steady rate from the mid- to late 1990s, after which their performance flatlined and then began a slow, decade-long decline that industry insiders refer to as big pharma’s “lost decade.” By 2009, their performance started to improve, for reasons that we’ll consider further in Chapter 2 (Section 2.6).

A much different narrative emerges for the smaller, more dynamic biotechnology companies. From the mid- to late 1990s, biotech also had a positive growth rate, but one with much more risk relative to the steady growth rate of the pharmaceutical index, as reflected in its comparatively large swings in value. However, starting in 2003—interestingly enough, around the same time that the human genome was completely sequenced—the growth rate of biotechnology accelerated and has remained high throughout much of the following decades.

From a financial perspective, it appears that biomedicine has reached a turning point. So why is funding still so hard to come by at the early stages of drug and device development? We can break down biomedical funding into private and public components. Public funding for early-stage biomedical research from sources such as the National Institutes of Health (NIH) has declined (Figure 1.4) for a variety of reasons, many of them political rather than economic or business-related. However, this decline may be reversed as political perspectives shift in response to the growing healthcare needs of an aging population in the United States and abroad, and in the aftermath of the COVID-19 pandemic.

Global funding from the private venture capital (VC) sector has been more cyclical, going through a long period of declining funding followed by a reversal in recent
Funding for the National Institutes of Health. U.S. government funding for biomedical research from 1950 to 2020, adjusted for inflation using the Biomedical Research and Development Price Index (BRDPI).

Profile of a Leading Healthcare Institution: National Institutes of Health (NIH)

The National Institutes of Health (NIH) is the primary agency of the U.S. federal government for biomedical and public health research. It’s part of the Department of Health and Human Services and is composed of 27 separate institutes and centers. With an annual budget of $42 billion as of 2020, the NIH encompasses 0.9% of the current operating budget of the United States.

The NIH as an institution traces its origin to 1887, when the Hygienic Laboratory was established at the Marine Hospital on Staten Island, New York, using the new field of bacteriology in a clinical setting. As a scientific institution, the NIH has been involved in both basic and applied research, including the development of new vaccines, new laboratory techniques and methods, and the first approved gene therapy in the United States. Six thousand scientists are employed in this intramural research, within the metaphorical walls of NIH, whose facilities are primarily located in Bethesda, Maryland.

The NIH has been even more influential in its extramural activities. Only 10% of the NIH’s federal funding goes to its own research, whereas more than 80% is disbursed through nearly 50,000 competitive grants to more than 300,000 researchers at more than 2,500 research institutions throughout the world. Approximately 17% of current biomedical R&D funding in the United States comes from NIH grants.
years. Between 2008 and 2015, the number of active biotech VCs in the United States decreased by about a quarter, from 201 to 153 (Table 1.1), and the global number of VC financings of private biotech companies in 2012 was the lowest it had been in nearly a decade (Figure 1.5). The decline in funding for translating research ideas to early-stage drug discovery and clinical development often prevents potentially lifesaving therapies from completing the journey from bench to patient bedside. In the field of translational research, this notoriously difficult funding challenge has been labeled the Valley of Death.

### TABLE 1.1 Number of active biotech venture capital firms in the world, by year and region.

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<td>Global total*</td>
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<td>222</td>
<td>238</td>
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</table>

*The global total is not the sum of all regions, as an investor involved in many regions counts only once in the global total.


### FIGURE 1.5


Source: Huggett (2013, 2014, 2015), Lawrence (2017), and authors’ calculations.
Although biotech VC funding has been rising between 2015 and 2021—spurred in no small part by the COVID-19 pandemic and the success of mRNA technology—there’s still a Valley of Death between the preclinical stages of R&D and clinical development. Why does the Valley of Death exist? Why would capital be scarce at the very moment humanity should be redoubling its efforts to cure diseases now that we have the means to do so? Part of the reason is the increasing risk, uncertainty, and complexity of drug development.

1.5 THE CHALLENGES OF DRUG DEVELOPMENT

The typical drug development process is outlined in Figure 1.6. It begins in the laboratory where research ideas are born, developed, refined, and tested on animals such as mice. Once a new therapy has matured to the point where it’s ready to be tested in humans, it enters clinical trials, which traditionally have three phases. **Phase 1 trials** usually consist of a small number of healthy volunteers or patients with the targeted disease/condition (typically 20–100). In Phase 1, the primary objective is to test for safety and appropriate dosage of the therapeutic. If successful (i.e., the therapy can be given safely to patients without serious side effects), the testing moves on to a **Phase 2 trial**, in which both safety and efficacy are evaluated in a larger group of volunteers (up to several hundred people with the targeted disease/condition). Assuming all has gone well in Phase 2, the therapy is then tested in a **Phase 3 trial**, in which safety and efficacy are evaluated in an even larger sample of patients (typically 1,000–5,000). In total, these clinical trials can take about 6–7 years to complete. With early-stage research and the FDA review process factored in, however, the entire process for a new drug to be approved can take as long as 10–15 years.

Three issues make funding these projects difficult. First, they’re expensive, costing hundreds of millions of dollars or more to take a potential therapy from preclinical animal models all the way through Phases 1–3 and FDA approval. Second, it takes years of testing before they generate revenue. Third, and perhaps most important, the probability of success at the end of this 10- to 15-year process is very low. For example, the historical odds of successfully developing an anti-cancer compound from Phase 1 to FDA approval are about 1 in 20. The combination of these three features of cost, duration, and long odds presents a nightmare scenario for the typical investor. Moreover, the efficiency of the process seems to be getting worse, as illustrated through an empirical relationship that has facetiously been called Eroom’s Law, which is Moore’s Law spelled backward (Figure 1.7).

Moore’s Law (first proposed in 1965) predicted that the computing power of a computer chip would double for the same cost every few years, a rising trend. The illustration of Eroom’s Law in Figure 1.7, however, shows that the number of new drugs approved by the FDA per billion dollars spent on R&D has halved roughly every 9 years (after adjusting for inflation).5 Because this is a logarithmic plot, we see that the downward efficiency of the industry has been getting exponentially worse for decades.

5In 2020, Ringel et al. (2020) reported some promising new evidence that we may finally be reversing Eroom’s Law.
**FIGURE 1.6**

**The drug development process.** The path by which a drug is developed from preclinical drug discovery through clinical trials and FDA approval is a lengthy, complex, and financially risky process that involves multiple stakeholders and several discrete phases of R&D and clinical testing.

![Diagram of drug development process](image)

**Pre-discovery: Basic research and screening**

- **Tens of thousands of compounds**
- **IND submitted**

**Drug discovery**

- **3–6 years**
- **Number of volunteers**: 20–100

**Clinical trials**

- **6–7 years**
- **Number of volunteers**: 100–500

**FDA review**

- **0.5–2 years**
- **Number of volunteers**: 1,000–5,000

**Scale-up to manufacturing**

- **Phase 4 / Ongoing research and monitoring**
- **NDA submitted**

*Figures for number of volunteers are approximate.*

**FIGURE 1.7**

**The growing inefficiency of the drug development process as depicted by “Eroom’s Law.”** The number of new drugs approved each year per billion dollars of R&D spending has halved roughly every 9 years.

![Graph showing the decline in the number of drugs produced](image)

Average number of drugs produced

*Source: Scannell et al. (2012) updated in Jones and Wilsdon (2018), and authors’ calculations.*
One reason for this trend is that drug development is apparently becoming more difficult.

**Example 1.1:** To understand why drug development is becoming more difficult despite (and perhaps because of) improvements in science and technology, consider the following example. Combination therapies, which treat a single disease using multiple medications, have been shown to work remarkably well for certain diseases. The best-known example of a combination therapy is the so-called AIDS “cocktail” of five anti-retroviral drugs, known collectively as highly active anti-retroviral therapy (HAART). Individually, these drugs aren't particularly effective against HIV. But when used together, they turn a death sentence into a chronic but manageable condition for millions of people around the world. It would be hard to overstate the impact that HAART has had on humankind.

Now that we're armed with the scientific knowledge that combination therapies can work much better than single drugs or monotherapies, shouldn't we try treating other diseases with combinations as well? In fact, certain biomedical experts have argued that we don't need more new drugs; they claim that we should be able to deal with *all* human diseases with the drugs we already have, if we can find just the right combination. How hard could that be?

Suppose we could treat each human disease using a unique combination of just two drugs, and we had at our disposal all the existing drugs that have already been approved. As of 2019, there are about 3,700 drugs in total. How many unique pairs of 3,700 drugs are there? The precise mathematical answer is 6,843,150. To search through all possible pairs to find just the right combination would require nearly 7 million clinical trials, each costing hundreds of millions of dollars, taking a decade or longer to complete, and requiring thousands of patients which, across all 3,700 drugs, would involve more subjects than the total population on the planet.

This example should give you some sense of the complexity of the problem. Continuing with the calculation, we find that we can form approximately 8.4 billion unique triplets if three drugs were needed, 7.8 trillion unique quadruplets, and 5.8 quadrillion unique quintuplets of drugs for possible combination therapies. In addition, we would need to consider dosage regimens, biomarkers (i.e., traceable substances whose detection can be used to monitor health), side effects, and other variables in counting the different types of trials we would need to conduct. Very quickly, the search space becomes immensely large—let's just call it gazillions 😃!

This simple thought experiment shows that as biomedical research becomes more complex, drug development can become less efficient, making the odds of success even lower. This increased risk makes funding translational biomedical projects less attractive to investors.

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6See https://www.drugbank.ca/stats.
CHAPTER 1

WHAT DO INVESTORS WANT?

We saw in the previous section that drug development projects are costly, lengthy, and have a low probability of success. To understand why these features are so unattractive to investors, consider the following two observations.

Observation 1: There’s a trade-off between risk and reward.

Figure 1.8 displays the cumulative returns of a $1 investment in four different unnamed financial securities over an unspecified investment period. To gauge your own behavior toward risk and reward, choose one—and only one—of these four securities in which to invest all your retirement assets. The green investment turns $1 into $2; not very rewarding, but not particularly risky. The red investment turns $1 into $4.50, way more rewarding but also quite a bit riskier given its ups and downs over time. The blue investment is the most rewarding of all at nearly $8, but also the most risky. And finally, the black investment is somewhere in the middle, with a return of $6.75 and less risk than the red and blue investments. Before reading on, please make a choice so that you’re invested in this example! Which one would you prefer if you had to choose only one of these investments to put your life savings in?

When typical investors are confronted with this choice, most of them select the black investment because it seems to have the best trade-off between risk and return—not as risky as the other investments but still reasonably rewarding.
To see how you fared, take a look at Figure 1.14 at the end of this chapter, which reveals the identities of these four investments and the time period (from October 1990 to October 2008), as well as their performance since 2008. The green investment is U.S. Treasury bills, the safest asset in the world, but not particularly rewarding, yielding virtually nothing since 2008, as Figure 1.14 shows. The red investment is the S&P 500 U.S. stock market index which, at $21.15 in December 2020, does considerably better than Treasury bills, so congratulations if you chose this asset. The blue investment is the big pharma company Pfizer, the best performer of all at $27.50. Finally, the black line—the most popular choice by far—is the Fairfield Sentry fund, the feeder fund for the Bernie Madoff criminal Ponzi scheme, which collapsed after October 2008, so if you chose this asset, condolences for getting wiped out!

Like a moth to a flame, most of us are drawn to investments that have high return and low risk. Financial analysts have a measure of this tendency, and it’s known as the Sharpe ratio (which we’ll study in more detail in Chapter 7), defined as the ratio of an asset’s excess expected return ($E[R]$) above the U.S. Treasury bill return ($R_f$) to a measure of its riskiness, which is usually the standard deviation of the asset’s returns ($SD[R]$):

$$\text{Sharpe} = \frac{\text{Reward}}{\text{Risk}} = \frac{E[R] - R_f}{SD[R]}$$

(1.1)

It’s human nature that investors are drawn to high Sharpe-ratio investments. The Sharpe ratios of the three risky assets in Figure 1.8 are 0.39 for the S&P 500, 0.44 for
Pfizer, and 2.89 for Fairfield Sentry (at least on paper, before it blew up). Based on your own choice, it should now be clear how the Madoff Ponzi scheme grew to approximately $50 billion, the largest fraud in the history of financial investment funds. One of the challenges to the biomedical ecosystem is that as we develop more sophisticated ways of treating diseases, medicine becomes more complex, which increases the financial risk of biopharma investments and reduces their Sharpe ratios. As a result, investors decide to put their money in higher Sharpe-ratio assets. This leads us to our second observation about investor behavior.

**Observation 2: There’s a difference between risk and uncertainty.**

Consider an urn that contains 100 balls, 50 red and 50 black (Figure 1.9). Now suppose you pick a color, red or black, after which a ball is randomly selected from the urn. If the randomly selected ball matches the color that you chose, then you get $10,000; otherwise, you get nothing.

In this situation, it doesn’t matter which of the two colors you select, because you’ll always have a 50% chance of winning. How much would you be willing to pay to play a single round of this game? When finance students are asked this question, the highest bid is often a little less than $5,000, which is the expected value from playing the game ($50\%\times$10,000 + $50\%\times$0 = $5,000).

Now consider Urn B, which also has 100 balls, but now you don’t know the proportion of red to black. In fact, your opponent gets to choose the proportion in the turn beforehand. Other than that single difference, the rest of the game is played in exactly the same way. How much would you be willing to pay to play a single round of this game? Despite that the odds of winning or losing are precisely the same in this game as in the previous case in which you know the proportion of red and black balls (50/50 odds of choosing the winning color from both Urn A and Urn B), most people will offer much less to play a single round of this game. How much less? Typically, as much as 40% to 80% less. Why?

When subjects are asked why, they explain that in the first case, they know the odds. In the second case, the odds are unknown and the fact that their opponent gets to choose the proportion is particularly troubling. Despite the fact that there exists a strategy whereby the subject can guarantee that the odds are fair—simply flip your own fair coin and pick red if the coin comes up tails and pick black otherwise—subjects

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**FIGURE 1.9**

Risk versus uncertainty as illustrated through the Ellsberg Paradox. Pick a color, red or black, and if a ball drawn from Urn A, which contains 50 red balls and 50 black balls is your color, you receive $10,000, and if it isn’t your color, you receive nothing. How much would you pay to play this game just once? Suppose the same game is played with Urn B, which contains an unknown mix of red and black balls. How much would you pay to play this game just once?
still won’t pay as before because they say that they just don’t “feel as comfortable” when there’s uncertainty about the risk.

This example is the famous Ellsberg Paradox from psychology, and it underscores a key aspect of human behavior: there are two kinds of randomness, and we treat them very differently. Risk is defined as the kind of randomness that can be quantified, as in the case of the 50/50 urn. Uncertainty is defined as the kind of randomness that can’t be quantified, that is, the unknown unknowns. Humans view risk and uncertainty as tangibly different. From a financial perspective, uncertainty can have a substantial impact on how people value an investment that goes well beyond the standard statistical models used to evaluate investments—investors dislike uncertainty even more than they dislike risk.

**Example 1.2:** Consider the investment opportunity in an anti-cancer drug project depicted in Figure 1.10:

- $200 million up-front investment
- 10-year time horizon
- 5% probability of success
- If successful, $2 billion per year for 10 years until the drug’s patent expires, which, as we’ll see in Chapter 4, is equivalent to a single payment of $12.3 billion in Year 10

**FIGURE 1.10**

**Payout timeline for a hypothetical investment project.** Requires a $200 million up-front investment and has no cash flows until Year 10, a 95% chance of total failure, and a 5% chance of receiving $2 billion a year from Years 11 to 20 (which is equivalent to a single payout of $12.3 billion in Year 10).

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Would you be willing to invest in this project? For most people, this project is simply too risky. When you calculate the statistics, the project has a positive expected rate of return, but it also has a large standard deviation, implying a Sharpe ratio close to 0. Moreover, any model that forecasts 20 years into the future has a great amount of uncertainty.
Example 1.2 highlights the issues that affect biomedical R&D projects. They’re simply too risky, and as the risk and uncertainty increase, the behavior of the stakeholders responsible for new medicines changes. For example, biotech venture capitalists will respond by investing in fewer start-ups, focusing instead on scientists and entrepreneurs with proven track records, well-established therapeutic areas, and assets in later stages of development. Pharma companies will respond by de-emphasizing in-house drug discovery efforts in favor of partnering with or acquiring smaller biotech companies that have reached certain milestones of demonstrated success. Entrepreneurs will respond by avoiding more speculative technologies in favor of areas that are currently “hot,” and may decide to forgo entrepreneurial ventures altogether in favor of safer positions within large corporations. And even government agencies such as the FDA or the NIH will respond to increased risk and their own funding shortages by favoring safer, albeit less transformative, medicines and research agendas.

Table 1.2 summarizes the drivers of increasing risk and uncertainty among these stakeholders and their predicted responses, a number of which have already been observed in practice. These trends and tendencies explain how the efficiency of the biopharma ecosystem is so closely tied to issues related to funding. In fact, more often than not, financing ends up driving scientific research agendas, as illustrated by the next example.

**Example 1.3:** Consider a $200 million investment opportunity in the following two projects:

- A “me-too” cancer drug that offers only incremental benefits relative to the current standard of care. It’s already in Phase 3 clinical trials and is likely to be approved. Moreover, it will immediately begin generating revenues once launched, because the law currently states that a substantial portion of the treatment costs of any cancer therapy must be reimbursed, regardless of
whether it offers real transformational improvements or incremental benefits, as long as a physician prescribes it to a patient.

- A combination therapy that consists of a newly developed drug that treats acute lymphoblastic leukemia and a second chemical compound. This combination has the potential to be a transformational therapy, one that could possibly cure the disease, but you haven’t yet identified the second drug.

In which of these two projects would you choose to invest your retirement assets? Most people select the “me-too” drug because it’s safer, and thus more likely to be profitable. This type of decision has been happening across the industry and is another contributing factor to the Valley of Death.

As risk and uncertainty increase, investors will demand higher rates of return. A study conducted by Cockburn and Lerner (2006) found that investors expect about a 20% per year rate of return from smaller biotech companies to compensate them for the risks of these early-stage projects. Figure 1.11 shows that biotech has sometimes performed extraordinarily well relative to this 20% hurdle rate (i.e., the minimum rate of return on an investment required by investors to compensate them for the level of risk), but in more recent periods, has generally underperformed.

In contrast, a similar study conducted by Giaccotto et al. (2011) found that investors expect a 10–15% per year rate of return from pharmaceutical companies. These

**FIGURE 1.11**

Biotech VC pooled internal rate of return (IRR) from 1996 to 2018.

![Graph showing biotech VC pooled internal rate of return (IRR) from 1996 to 2018. The graph illustrates the percentage of pooled IRR per year with a 20% hurdle rate line.](image-url)
companies are larger, more established, and more diversified than the smaller biotech firms, which helps to explain their lower hurdle rate (and subsequently allows them to raise funds from investors at more favorable rates, also known as their cost of capital). However, across all sectors in the economy, only 10% of U.S. companies have hurdle rates above 10% per year (Figure 1.12), so we see that funding for pharmaceutical companies is still expensive relative to other industries. We say that their funding is expensive, and the cost of capital is high because, when these companies go out to raise money, investors will demand a higher interest rate on their debt or greater concessions on the price of their equity to compensate them for the higher level of risk. As an analogy, consumers with higher credit scores tend to pay back their debts on time more consistently, so they typically get charged lower borrowing rates (we would say they have a lower cost of capital).

Is there a way we can reduce the risk of early-stage biomedical projects and, consequently, the cost of capital for these projects?

**Concept Check 1.** Which of the following does NOT characterize a typical investment in a biopharma project?

a. Investments can be very large.
b. Investments are illiquid (i.e., they can’t easily be sold or converted into cash).
c. Investments have a short time horizon.
d. Investments involve both risk and uncertainty.
1.7 FINANCIAL ENGINEERING CAN HELP BRIDGE THE VALLEY OF DEATH

Because the cost of capital is linked to an investment’s degree of risk—greater risks require higher rates of return so as to compensate investors for taking on such risks—the way to reduce the cost of capital is simple: reduce the risk. This is one of the primary objectives of the field of financial engineering, a collection of mathematical, statistical, and computational models and tools focused on measuring and managing the risks and rewards of all types of investments, including drug development projects. You may have come across some of these models and tools if you’ve ever taken an economics or finance class, ideas such as portfolio theory, mean-variance optimization, and securitization. We’ll discuss these ideas in more depth in the chapters to come. But for now, let’s consider a simple illustration of the power of financial engineering to reduce the cost of capital for drug development.

Consider combining 150 anti-cancer drug projects like the one outlined in Figure 1.10 ($200 million cost, 10-year horizon, and a 5% success rate) into a single financial investment, called a portfolio. This portfolio is similar to a mutual fund, which is a single legal entity that owns a collection of investments on behalf of its shareholders. As a shareholder of the mutual fund, you own a fraction of each and every security in that fund. So, in our example, a single legal entity owns 150 anti-cancer drug projects, and investors can then buy shares of that entity.

But if investors aren’t interested in investing in one of these projects, why would they want to invest in a fund that owns 150 of them? The answer to this question is critical because we’re going to need $200 million × 150 = $30 billion to fund our cancer fund. Given this large sum of capital required, our fund will need to be highly attractive to investors. It turns out that if these 150 projects are statistically independent—meaning that the success or failure of one project has nothing to do with the outcomes of any of the other projects—then we can show that the overall annualized standard deviation of the portfolio decreases from an incredibly volatile 423.5% to only 34.6%, while the expected return remains the same at 11.9%, implying a Sharpe ratio of about 0.34. In contrast, the Sharpe ratio for just one of these projects is only 0.03. By investing in a portfolio of 150 of these projects, and assuming they’re independent, we’ve managed to reduce the risk by an order of magnitude!

This feat is the result of diversification, the financial equivalent of not putting all your eggs in one basket. As a result, the kind of return that investors demand will be significantly lower for this portfolio, allowing us to attract more capital.

In fact, in this specific instance, we can actually raise most of the $30 billion needed by issuing bonds, which are similar to mortgages, auto loans, and other forms of borrowing, rather than through the traditional biotech funding route of venture capitalists and initial public offerings of shares of stock. With a 5% probability of success for each project and assuming independence, the probability that at least three of the 150 projects will be successful is about 98%. If we assume that each of the three successful projects is worth $12.3 billion (see Example 1.2), then there’s a 98% probability the portfolio will be worth $3 × $12.3 billion = $37 billion in Year 10. What if we borrowed money to fund this portfolio by issuing IOUs, or bonds, that promised to pay back a certain amount of money in Year 10, after our drug development projects
mature? How much could we borrow? Well, if we issued IOUs that promised to pay up to $37 billion in Year 10, we have a 98% chance of being able to make good on that promise, or a 2% chance of defaulting. As of September 9, 2021, the market interest rate for loans with a 2% chance of defaulting was about 1.76%, and we’ll learn from Chapter 3 that a 10-year loan involving a payment of $37 billion in Year 10 with an interest rate of 1.76% would give the borrower proceeds of $31.1 billion today in exchange for that IOU. Thus, the $30 billion needed can be easily obtained from bond markets, which are larger than any other source of capital by at least one or two orders of magnitude. For example, in 2020 the size of the U.S. corporate bond market was about $10.6 trillion (Figure 5.1). In comparison, the total assets under management in the entire VC industry in 2020 was just $548 billion, and the amount deployed in the pharma and biotech sector in that year was $28 billion. If we need $30 billion for a cancer megafund, we have to look beyond VC funds.

By using financial engineering techniques to reduce the risk, we can access entirely new funding sources like bond, private-equity, and derivatives markets, which we’ll describe in greater detail in the coming chapters.

A warning: This analysis relies on the assumption of statistically independent projects, that is, we’ve assumed that the outcome of one project won’t affect the outcome of any other. There are all sorts of reasons why this assumption may not hold true, not the least of which is that science is a very interconnected process. Figure 1.13 shows the probability of at least $k$ successes among the 150 projects, using different assumptions for the pairwise correlation of success/failure between projects. As this
pairwise correlation increases from 0% (which is the case of independence, depicted by the blue line) to 10% (orange line) to 40% (green line) to 80% (purple line), the benefits of diversification decline and the probability of having at least three successful projects decreases. As a result, the cost of capital doesn’t decrease as much as before, and we can no longer raise as much capital.

Figure 1.13 demonstrates the importance of diversification, that is, spreading investments across very different and, to the greatest extent possible, independent projects. Companies that crowd around the same therapies and technologies are like young and inexperienced soccer players who all crowd around the ball. Soccer coaches have to remind these novices to spread out and go to where the ball will be, not to where it is now. Similarly, diversification—the idea of spreading the risk across uncorrelated projects—can help the biomedical industry to reduce its cost of capital and reach its goals with higher likelihood.

At the time of writing, interest rates are at near-record lows, yet we still have many promising research programs that can’t raise the money to develop the cures that patients desperately need. A large part of this textbook will be devoted to understanding this conundrum and to developing the tools that will allow us to create new financing structures and business models that can be used to bridge this Valley of Death. Financial engineering can play an important role in accelerating biomedical innovation.

**Example 1.4:** In 2009, the Defense Advanced Research Projects Agency (DARPA), a research organization of the U.S. Department of Defense, ran a competition known as the “DARPA Network Challenge” in which it placed 10 large, red weather balloons in random, fixed locations all across the United States. The contest stated that the first person or team to identify the GPS coordinates of all 10 balloons would win a cash prize of $40,000. A group of MIT students led by Professor Alex Pentland won the challenge, and they won it in an astonishingly short amount of time: it took the team only 8 hours and 52 minutes! How did they accomplish this amazing feat? Financial engineering.

In addition to concentrating their efforts on social networks, the MIT team came up with a specific reward mechanism to recruit collaborators to help them. They announced publicly on a website that if they won the $40,000 prize, they would pay out all of it to those who helped them win. But they were very explicit about how they were going to do this. The team’s stated plan was to pay out $4,000 for each balloon, but in the following way: they would pay $2,000 to the first person to send them the location of any balloon they hadn’t already located. However, they also proposed to pay half that amount, $1,000, to the person who recruited the person who sent them the location of any balloon they hadn’t already located. If you recruited someone who recruited someone who was the first to send the MIT team the location of a balloon they hadn’t already located, you would receive half of $1,000 or $500. And so on. For each degree of separation from the first person who sent them the location of a balloon they hadn’t already located, you would receive half the amount of the money promised to the person with the next lowest degree of separation.
This beautifully engineered algorithm for incentivizing people to help them with this task had three key features: (1) it rewarded collaborators in proportion to how helpful they were in identifying the location of a balloon, so they had every incentive to recruit as many people as possible to maximize their chances of getting paid something—literally everybody got paid something; (2) it was totally credible in the sense that the amount of money promised added up exactly to the prize money they would receive if they won (in particular, you can show through some simple algebraic manipulation that $2,000 + $1,000 + $500 + $250 + \cdots = $4,000, and 10 balloons at $4,000 each is $40,000); and (3) it was totally transparent—everyone knew ahead of time what the rules were and where they stood relative to other collaborators. By the end of this process, the MIT team managed to recruit more than 10,000 participants in this network in less than 9 hours.

Financial engineering can provide just the right incentives to mobilize large groups of people to collaborate on a given task. In this textbook, we’ll explore how new business models and innovative financial structures can be used to motivate biomedical stakeholders to collaborate in the search for new medicines and cures in a similar fashion. Imagine if literally everyone in the world were incentivized to help develop new therapies for patients in need.

1.8 ROADMAP

The primary goal of this textbook is to explore how tools from financial engineering can be used to fund innovation in the life sciences more efficiently. These tools can be applied to other industries that have similar challenges, such as clean energy, infrastructure, and geo-engineering solutions to global warming, but our focus will be exclusively on biomedical applications.

The book is divided into two parts. The first half, Chapters 1–7, provides the reader with tools from modern financial analysis that are particularly relevant for the life sciences. In particular, we’ll cover the healthcare industry from a systems perspective (Chapter 2); present value relations (Chapter 3); evaluating business opportunities (Chapter 4); valuing bonds (Chapter 5) and stocks (Chapter 6); and portfolio management and the cost of capital (Chapter 7).

The second half of the book focuses entirely on biomedical applications, with an emphasis on new business models and structures. We’ll explore drug and device development and clinical trials (Chapter 8); decision trees and real options (Chapter 9); Monte Carlo simulation (Chapter 10); healthcare analytics (Chapter 11); biotech venture capital (Chapter 12); securitizing biomedical assets (Chapter 13); and pricing, value, and ethics (Chapter 14). We conclude with an extended case study of the drug royalty investment company Royalty Pharma that brings together many of the concepts covered throughout this textbook (Chapter 15).

Healthcare finance is evolving even as you read this. No single individual really understands all aspects of this complex and dynamic industry. Only through collaborations among all key stakeholders in the biomedical ecosystem will we be able to solve
the challenges facing healthcare in the 21st century. The ideas developed in this textbook are meant not only for business school students interested in the life sciences, but also for life sciences and medical students and professionals who are interested in taking their research ideas and clinical expertise and turning them into lifesaving therapies. This textbook also provides patient advocates, investors, and portfolio managers an opportunity to use these new structures to help drive biomedical innovation. Many of these stakeholders view the financial system as merely a set of constraints to their activities, never considering the possibility that this very same system contains powerful forces that can be harnessed to help them achieve their own objectives more effectively.

This strange admixture of finance and healthcare may be offensive to some readers—after all, who but an economist would even think of considering investment return on investment and financing decisions in the context of life-and-death issues like cancer drug development? We understand. Like many of you, we’ve lost friends and family members to cancer and other diseases. But we’re convinced that the only way to make system-wide improvements in how therapeutics are developed is to be as objective and practical as possible about the financial challenges of the biopharma industry. By examining the drug development process from all the major stakeholders’ perspectives, we can begin to determine the greatest roadblocks to biomedical innovation and propose methods for getting around them.
But the most important perspective of all—and the one that underlies all of our efforts in healthcare finance—is the patient perspective. Tremendous fortunes are possible in this sector, but much more importantly, there are hundreds of thousands of patients who are now being helped by these new therapies, and millions more who are still waiting. Finance doesn’t have to be a zero-sum game if we use it wisely. We can do well by doing good, and our hope is that this textbook will motivate a new generation of students to enter the exciting and immensely rewarding field of healthcare finance.

CONCEPT CHECK ANSWERS

Concept Check 1. The answer is c: Investments in biopharma projects usually have a long time horizon. New therapies take time to be researched, developed, tested clinically, reviewed by regulatory agencies, and so forth. We study the drug development process in more detail in Chapter 8.

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