Health care firms benefit from consistent demand, as well. Even when the economy is in the tank, people still get sick and need doctors and hospitals. As a result, the health care sector has traditionally been a defensive safe haven.

The health care sector includes drug companies, biotechs, medical device firms, and health care service organizations. Of all these areas, we think drug companies and medical devices firms are usually the most promising because they typically have the widest economic moats. However, investors often get swept away by these companies' heady growth rates, so valuations can be steep.

Economic Moats in Health Care

Health care companies often benefit from economic moats in the form of high start-up costs, patent protection, significant product differentiation, and economies of scale. This makes it tough for new players to enter the market, particularly for drug companies with valuable patent rights, managed care organizations with large provider networks, or medical device firms with long clinical track records. These characteristics make for great profitability: The market-weighted return on equity for health care firms has averaged 23 percent over the last five years, despite the economic recession.

For example, in big pharmaceutical companies, patent protection often prevents direct competition, so firms charge the highest price the market will bear for prescription drugs. And because most costs are paid by insurance plans, there's even less price sensitivity for the end consumer. These higher prices—combined with economies of scale—have led to gross margins often surpassing 75 percent to 85 percent.

Size is another barrier to entry for drug companies. Developing a single drug can take 15 to 20 years to get through the entire research, development, and regulatory process and can cost hundreds of millions over that time frame. Few scientists and entrepreneurs have access to that kind of capital. Even if they surmount the time and money hurdles, going head-to-head against a Pfizer or Merck when selling to physicians requires a large salesforce and lots of advertising dollars. In contrast to, say, software or restaurants, where start-up costs are low and new entrants spring up frequently, consolidation has been the trend for many health industries in the last several decades, and established players usually have an edge. Smaller firms often can't compete.

Health care's vast size and rapid expansion makes investing in the sector look like a no-brainer. But it is also fraught with complex relationships, intense controversy, and political pressures to regulate who gets what and who pays for it. Unlike clothing, computers, or consulting services, health care consumers are frequently not the ones writing the check for the products and services they use, and many times they aren't even the ones making the buying decision.

Whereas Wal-Mart shoppers can easily see which brand of paper towels is cheapest and works best on big spills, pricing is often opaque to health care consumers and irrelevant to physicians helping make the decisions. Thus, there is little incentive to shop around for the best price to keep costs lower. (This trend has shown some signs of changing, as companies have been shifting a greater percentage of the health care burden to their employees. But overall, price generally isn't the primary consideration for a patient seeking medical care or a doctor prescribing a drug.)

In the following sections, we explore the dynamics and trends of some of the major health care industries. We won't cover every corner—health care is too broad and diverse to cram everything into a couple of dozen pages—but we'll introduce you to the sector's biggest industries.

Pharmaceuticals

Big pharmaceutical companies typically have wide moats and some of the most attractive financial characteristics of any industry. Branded pharmaceutical companies (as opposed to generics, which have a lower return business model) generally boast top-notch profit margins. Most global pharmaceutical companies have returns on invested capital (ROICs) in the mid-20s. Top-notch companies such as Pfizer are often in the 30s. Drug-company margins are also worth salivating over, with gross margins often near 80 percent and operating margins between 25 percent and 35 percent. What's more, drug companies offer plentiful free cash flow and virtually debt-free balance sheets.

But innovation isn't cheap. It takes money to make money, and the average cost of taking a drug from discovery to the pharmacy shelf is $800 million. Only a third of those drugs ever return their costs of development. Plus, drugs take years to develop. The clinical testing phase (trials in humans) alone can take a decade. All the while, the company is pumping money into the research process with no guarantee of a return.

There's also budgetary pressure in the United States to reduce health care costs, specifically the dollars spent on prescription drugs. Since 1980, prescription drug costs have increased faster than every other health care cost, almost doubling as a percentage of total health care dollars, from 4.9 percent to 9.4 percent. But if political pressure leads to lower drug prices (as a Medicare prescription drug plan might), big pharma could see its margins come down.

Demystifying the Drug Development Process

Drugs are discovered in many different ways. Sometimes they're discovered by mistake, like Viagra. (Pfizer scientists noticed the "side effect" from a blood pressure drug.) Other times, they're discovered only after an exhaustive process of testing thousands of compounds in petri dishes and lab rats. This process of identifying possible targets and determining whether they should move down the development chain can take five years or more and cost in the hundreds of millions of dollars.

With new technology and supercomputers, scientists are finding ways to "virtually" test molecules against different genes to narrow the number of compounds before they start testing in live animals. But for now, drugs still go through years of initial research before being tested in mice, let alone humans.

Drugs typically take the path outlined in Figure 14.1 before they get to the pharmacy shelf.

Preclinical Testing: This animal testing phase is called *preclinical testing.* The primary objective is to evaluate potential toxic effects. Before a drug gets anywhere near a human, scientists must have a clear understanding of the possible damage it could do. It takes two to three years on average to discover a viable drug candidate and another year to find out if it is fit for human testing. For the small percentage of drugs that survive, an investigational new drug (IND) application is filed with the Food and Drug Administration (FDA). Approximately 85 percent of INDs move on to Phase I.

Human Clinical Trials (Phase I): Phase I is the first of three stages of human clinical testing. In Phase I, a drug is tested in a small group (fewer than 100) of healthy volunteers with the goal of gathering initial data on safety and efficacy—whether the drug has the ability to produce the desired

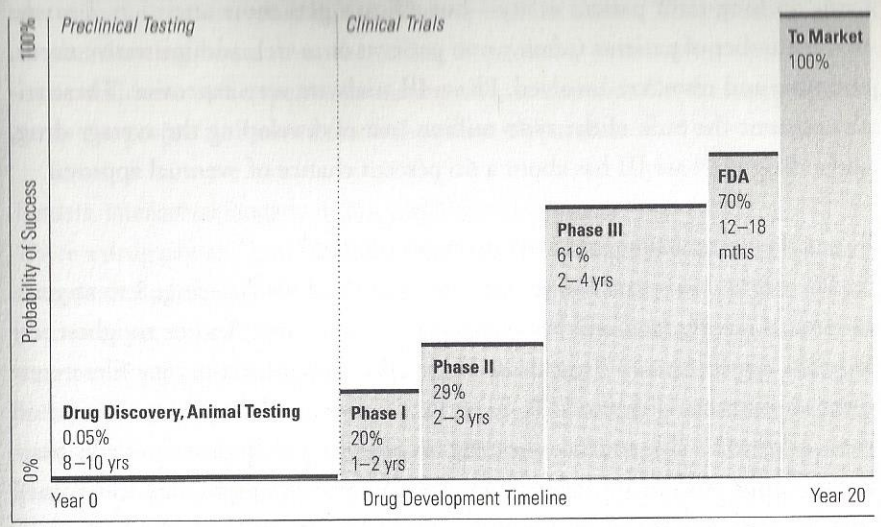

Figure 14.1 Drug development timeline and cumulative probability of success. *Source:* Professor Alicia Loffler, Kellogg School of Management and Biochem Pharma 1998 Annual Report.

effect. Safety is the number-one concern here, though scientists and physicians also evaluate the body's reaction to the drug. A drug in Phase I has only a 20 percent chance of eventual approval but can still cost a few million dollars, including the cost of development, clinical trials, and continuous communication with the FDA.

Human Clinical Trials (Phase II): In Phase II, the drug is tested in a larger population (usually 300 to 500) of patients afflicted with the targeted disease to get a more comprehensive profile of how well the drug works. The managers of these trials use them to compile additional data on safety and side effects. Here, physicians and scientists test for how much of the drug to give and how often to give it. This phase often costs more than $5 million, and more than half of all drugs in Phase II fail to move to the next phase.

Human Clinical Trials (Phase III): The final testing hurdle is Phase III. These trials involve testing the drug in a much larger group of afflicted patients over longer periods. Safety is still an issue—Phase III trials are the first trials to

focus on long-term patient safety—but efficacy gets more attention. Because of the number of patients (often 5,000 patients or more), administrative needs, and time and resources involved, Phase III trials are very expensive. These trials consume the bulk of the $800 million cost of developing the average drug, and a drug in Phase III has about a 60 percent chance of eventual approval.

Role of the United States Food and Drug Administration

So far, a drug has spent two to three years in preclinical testing, 8 to 12 years in clinical testing, and still hasn't brought in dime one. And its toughest test is still to come. Once a drug clears Phase III testing, the company files a new drug application with the U.S. FDA (and other regulatory agencies around the world) to be able to place the drug on pharmacy shelves and actually market the drug. An FDA filing is a tome that may weigh more than some small cars, so preparing it can take months. According to PhRMA, the U.S. pharmaceutical industry's trade group, it takes about 17 months for the FDA to review an application, and a drug under review with the FDA still has only about a 70 percent chance of approval.

Each filing typically seeks approval in a single (and highly specific) indication. For example, Rituxan is a drug approved to treat specific types of lymphoma patients who no longer respond to other forms of treatment. Once Rituxan was approved, that particular indication was the only one for which its maker can market the drug (although physicians can prescribe it for anything they choose, often referred to as "off-label usage").

The FDA has advisory committees that meet several times per year to discuss the applications. These committees submit their opinion to the FDA, which then decides the fate of the drug. The FDA can exercise any number of judgments for a new drug application, including granting marketing approval (which means the company can market the drug for the specified indication), requesting additional data or another round of testing, or denying the application.

The last outcome is definitely bad for the company filing the application. It comes as a "not-approvable letter" and means that the information in the filing did not convince the FDA of the drug's merits. It's not always death for the compound, however. Drug applications can be re-filed, but if an application gets all the way through the FDA review process and is rejected, it's likely

the company has no more information to back its claims. That means it's back to the drawing board. Another filing is probably years away, and millions more will have to be spent researching the compound. Or the company can scrap the project and move on. Either way, it's painful.

Patents, Intellectual Property Rights, and Market Exclusivity

Once a drug gets the nod from the FDA, the marketing can begin. Brand name drugs enjoy patent protection for 20 years from the date the company first completes the patent application (or 17 years from the issue date). However, because a patent application is usually filed as soon as a drug is identified and not when it hits the market, drugs rarely enjoy 20 years of monopoly profits because a significant portion of the protected period is eaten up by trials and the approval process. Many drugs enjoy only 8 to 10 years of patent protection after they are launched in the marketplace. During that period, no other company can market the same chemical compound, although competitors are still free to develop different compounds that treat the same condition.

To find out about a drug company's patent protection, look at the 10-K report, under the section titled "Patents and Intellectual Property Rights." You should find a discussion of the company's patents and when they expire, but because drug companies often engage in fierce legal battles to try to extend their patents, you'll likely need to visit the company's Web site for complete information. The 10-K also discusses any pending lawsuits, which can be a sign of trouble on the horizon.

Generic Drug Competition

After a drug goes off patent or loses market exclusivity, whichever comes later, the field is open to competition from generic medications. Generic drugs have the same chemical composition as brand name drugs but cost significantly less—usually 40 percent to 60 percent less. Generic drug makers can charge much less because they don't have to recoup the $800 million in per drug research and development costs. And for most drugs, the manufacturing costs are nominal (20 percent to 25 percent of sales), so the price can be nominal as well.

The entrance of a generic competitor in the United States can be devastating for its brand name counterpart. Drugs have been known to lose as

much as 80 percent of their sales in the first six months after going off patent. Eli Lilly's famous depression drug, Prozac, is a case in point. In 2001, when Prozac lost its patent protection, the drug's quarterly revenues dropped from $575 million in the second quarter to $96 million two quarters later. So if you're considering buying shares in a drug company that depends on a specific drug for a significant percentage of its sales, don't bank on the money continuing to come in after the patent expires.

Hallmarks of Success for Pharmaceutical Companies

Branded pharmaceutical companies have historically offered high margins, little debt, and cash flow galore. To find companies that can continue to provide stellar performance, focus on these traits:

- *Blockbuster drugs* (typically defined as drugs with more than $1 billion in sales): Companies with blockbusters gain manufacturing efficiencies by spreading fixed costs over more products. Selling the drug at high prices, driven by strong demand, inflates a drug maker's profitability and provides more bang for the buck. Pfizer is the perfect example: In 1997, only two Pfizer drugs had annual sales greater than $1 billion, but by 2002, eight drugs surpassed the $1 billion mark, with four drugs breaking the $2 billion mark. Thanks in part to these blockbusters, Pfizer's operating margins improved from 20 percent in 1997 to 38 percent in 2002.
- *Patent protection:* All drugs eventually lose patent protection, but the companies that manage those losses the best will generally provide investors with a steadier stream of cash flows. Bristol-Myers Squibb showed what can happen when a drug firm loses patent protection on large products without replacement drugs waiting in the wings. Between the second quarter of 2000 and the first quarter of 2002, Bristol lost the U.S. patents on three heavy hitters, and nearly 20 percent of the firm's total revenue evaporated in less than two years. On the other hand, when AstraZeneca's Prilosec was about to lose its U.S. patent in 2001, the company had already begun switching patients from the first-generation drug to the patent-protected second-generation version. By the time a generic competitor entered the market, AstraZeneca's new drug had established itself in the market and was bringing in 35 percent of the revenue of the first-generation drug.
- *A full pipeline of drugs in clinical trials (and the larger the population those drugs serve, such as cancer and arthritis, the better):* Merck is a decent model for this strategy. It generally has had an abundance of products in development and has directed research efforts toward unmet medical needs with millions of potential patients. Merck's five top-selling products in 2002 had a combined potential market of 138 million Americans.
- *Strong sales and marketing capabilities:* Physicians rely on pharmaceutical salespeople to learn about new products, and a salesforce that has successfully penetrated the physician market in the company's core therapeutic franchises already has physicians' ears and often their trust as well. Pfizer's relationship with cardiologists, Wyeth's access to gynecologists, and Eli Lilly's close ties with psychiatrists shouldn't be ignored. This expertise is so valuable that biotech firms often partner with large drug firms and give up a sizeable chunk of their profits just to leverage the marketing resources of their drug-company partners.
- *Big market potential:* Drugs that treat conditions affecting a large percentage of the population (such as erectile dysfunction, high cholesterol, depression, or high blood pressure) typically have better potential than niche products. So do drugs that treat chronic conditions, because patients must continue taking the medication to stay healthy.

All of this information can be found in the company's 10-K. Specific disease Web sites (such as the National Kidney Foundation or cancer.gov) also often have information on clinical trials and drugs available to treat a disease or disorder as well as the number of patients suffering from those diseases. Being able to analyze the depth and breadth of a company's drugs and development pipeline is half the battle when looking at pharmaceutical and biotechnology stocks. So, roll up your sleeves and dig into the 10-K to get the details on the strength of the company's drug pipeline.

Generic Drug Companies

Generic drug makers don't have the extraordinary margins of branded drug makers, but they are growing much faster as generic drugs become more

Common Investing Pitfall: Too Much Single-Product Risk

It might sound strange to view megablockbuster drugs as a negative, but they can become a disadvantage. If a drug's revenues become a large enough piece of the pie, a company's fate can be linked too heavily to that drug. Because that drug will eventually lose its patent protection, we think it's wise for investors to account for the *single-product risk* by demanding a slightly larger margin of safety.

Pfizer's Lipitor brought in a staggering $8 billion in sales for 2002. By the time Lipitor loses its U.S. patent protection in 2011, annual U.S. sales could easily be more than $10 billion. That's such a huge amount that it will be nearly impossible for Pfizer to fill the gap once generic competition hits. In addition, just five drugs pull in half the company's revenue. Megablockbusters such as Lipitor not only contribute large portions of total revenue, but also are often high-margin products. When the patent expires, the maker loses a chunk of revenue and its profitability usually declines as well.

popular. These copycat companies usually have gross margins in the 40 percent to 50 percent range, with operating margins around 15 percent to 20 percent. Returns on invested capital vary dramatically depending on the company's exposure to branded drugs. (Most generic drug makers also sell nonblockbuster branded drugs.) Teva Pharmaceuticals, the closest thing to a pure-play generic company, has ROICs around 10 percent, whereas Watson Pharmaceuticals, which generates a little more than half its revenue from branded drugs, has ROICs in the low to mid teens.

Ironically, generic drug companies can still benefit from some competitive barriers. The first company to file a legitimate patent challenge against a branded drug enjoys 180 days of marketing exclusivity, which allows the generic company to cash in before others join the party. The windfall can dramatically change the company's profitability in the short term; a 10-percentage point increase in operating margins isn't uncommon. Once the multitude is allowed to join the fray, the only company that comes out ahead is the low-cost manufacturer. Given the

crucial importance of manufacturing scale, you're usually better off with an established player in generic drugs.

Generic companies have benefited from some longer term trends. As of mid-2003, nearly 50 percent of all prescriptions were filled with generics, up from about 20 percent in the mid-1980s. This trend should keep moving up, thanks to the numerous drugs coming off patent each year, as well as pressure to rein in rising prescription costs. Even at lower margins, these drugs can be profitable with the right cost structure. Last, the political winds are blowing in favor of generic companies as politicians and the general public look for ways to lower health care costs.

Biotechnology

Although the best biotech companies can generate enormous free cash flow—biotech giant Amgen threw off more about $1.5 billion in free cash flow in 2002—most are too speculative for all but the most aggressive investors. Picking successful firms requires a bit of skill, some understanding of the science, and a lot of luck.

Biotechnology firms are often thought of as younger, hipper, more innovative, and faster growing than their pharmaceutical counterparts. They seek to discover new drug therapies using biologic—cellular and molecular—processes rather than the chemical processes used by big pharma. Biotech firms are also on the cutting edge of developing novel therapeutic products, using groundbreaking technology platforms such as proteomics and genomics.

However, biotech drug development is still all about probabilities, but with even more product risk because the therapies are often completely new forms of treatment. For example, Genentech has been developing a treatment that attempts to stop the body's mechanism for growing new blood vessels (a process called *angiogenesis*) on the theory that a cancerous tumor will die if it no longer receives blood. Although several companies are working on similar therapies, none have been successful to date. Even if they are successful, the true size of these markets is anyone's guess. This adds another layer of uncertainty to the drug development process—as well as volatility in stock prices.

Hallmarks of Success for Biotech Companies

Think about biotech firms in three categories: established, up and coming, and speculative.

Established: These are the bigwigs of biotech and include companies such as Amgen, Genentech, and Biogen IDEC, which each have annual product revenues of more than $1 billion and market capitalizations beginning to rival those of big drug companies. They generate positive earnings and cash flow, and their drug development pipelines are large enough to sustain decent sales and earnings growth. As these firms become larger, their future cash flows become less risky.

In this category, look for:

- Firms with a large number of drugs in late-stage clinical trials
- Plenty of cash on hand, plus cash flow to cover several years of research and development expenditures
- Firms that have built a salesforce of their own—so they no longer have to pay another firm to market their products and can begin to build relationships with physicians
- A stock price that provides a margin of safety of around 30 percent to 40 percent to its fair value

Up and Coming: Many biotech firms are on the cusp of success, either with a product on the market or within arm's length. Some are on the verge of breaking into the black, while others have already demonstrated small but positive earnings. In other words, they've got more than a cell in a petri dish, but they still have a lot to prove. All of these firms hold lots of risk and typically have a narrow economic moat or none at all, depending on competing products.

Cash is king during this stage, and these companies are often able to raise capital during the market's periodic biotech booms. But it's worth keeping an eye on how quickly they are spending that cash because the last phases of clinical trials are the most expensive, and preparing literally truckloads of documents for the FDA isn't cheap. That's why it often makes sense for up-and-comers to form partnerships with bigger pharmaceutical or biotech

firms. Although a partnership agreement means giving up a chunk of the profits, getting to market faster can be worth the cost.

Investors should ask the following questions to reduce their risk:

- Does the company have enough cash to get through the final (and most expensive) stages of testing? Compare the amount of cash on the balance sheet to the amount of cash that the firm burns through in a typical year. Phase III trials can cost tens of millions. Can the company write a check for these trials, or will it have to go outside for capital?
- Have larger biotechnology firms or pharmaceutical companies been willing to join forces with the firm? Partnerships can be a double-edged sword. They often validate the viability of a biotech's technology and provide knowledge and sales expertise, but they also take a huge chunk of the profits. For example, Biogen IDEC's cancer drug Rituxan has gone gangbusters since its 1997 approval, but because of the company's partnership with Genentech, Biogen IDEC sees only about a third of the drug's sales.
- Because future cash flows are so difficult to predict, does the stock price trade at a big enough discount to fair value to provide a margin of safety? A 50 percent margin of safety is reasonable given the risks of biotech.

Speculative: Newer biotech companies, which make up the majority of all companies in this industry, are too risky for the vast majority of investors. Although firms in this category undoubtedly have interesting technology and could be extremely successful some day, real revenues from real drug products are many years away, and positive cash flow from operations is even further out. Compound that risk with the slim odds that most early-stage drugs will ever reach the market, and we'd classify them as high-risk, no-moat stocks—which means we'd need a gargantuan margin of safety before we'd be willing to own them. These stocks are more like lottery tickets than anything else.

If you're doing research on a biotech company, the company's 10-K is the best place to start. Here, the company typically explains in layman's terms the technology and drugs in development and explains how the company is funding its research and partnerships. Disease Web sites cancer.gov and

MedicineNet.com and science journals often have information about drug classifications, market sizes, and competing and substitute products. In addition, industry resources such as the Biotech Industry Organization and BioSpace each have drug, company, and industry information.

Medical Device Companies

Medical device companies are probably the most straightforward of the health care industries. These are the companies that make the hardware, such as pacemakers and artificial hips, for medical procedures. There are two main types of device firms—cardiovascular and orthopedic—and they're well worth getting to know, given how many firms in this industry have wide economic moats.

As with the other health care sectors, the aging population and increase in life expectancy will drive sales growth in medical devices. Both the incidence of heart disease and the need for joint replacement rise substantially among older people. Also, now that physically active Baby Boomers are suffering from a few aches and pains of aging, physicians are starting to perform more joint replacement procedures in younger patients. Because a new hip has an average life of about 10 years, this should eventually expand the market for revision surgeries when the first hip wears out.

The ongoing pressure on medical costs also helps spur demand for some medical device companies, as new surgical techniques dramatically reduce the cost of some procedures by reducing the length of the associated hospital stay.

For example, traditional cardiac bypass surgery, aimed at increasing blood flow to the heart, involves a 10- to 12-inch incision down the chest, cracking open the rib cage, and approximately eight days in the hospital, followed by two months of recuperation. Less invasive cardiac bypass surgery is performed with a three- to five-inch incision between the ribs (or several one-inch incisions) and requires a three-day hospital stay and about two weeks of recovery time. What's more, minimally invasive procedures typically cost 25 percent less than the traditional open-heart bypass.

In addition to their attractive growth characteristics, device companies also typically boast wide economic moats. Economies of scale, high switching costs, and long-term clinical histories (in excess of 30 years for some orthopedic devices) all serve as high barriers to new entrants. As a result, a few major

players dominate both the cardiac and orthopedic device markets. Patent protection on devices and instrumentation used for installation also provides a measure of protection from competitors for each company.

Switching costs tend to be high for orthopedic devices because physicians are often reluctant to drop one firm's devices in favor of another's. Installing an artificial hip or knee is complicated, and the procedures require specialized tools and training. Because each company makes its own proprietary set of tools that work exclusively with its own joint replacements, a surgeon who decides to use a different company's artificial hip must squeeze in time to receive training on how to use the new instrumentation system. Given how busy surgeons generally are, that's unlikely to happen unless the new joint is significantly better than the one the surgeon is currently using. It also takes time to complete enough procedures to become comfortable with the new system.

Medical device companies hold a great deal of pricing power as well. Medicare and insurance companies have so far been reluctant to limit brand choices when it comes to joint replacements and pacemakers, which has allowed orthopedic device makers (for example) to consistently raise prices by 3 percent to 5 percent each year.

Finally, some device firms face less risk than pharmaceutical firms because product improvements tend to be evolutionary rather than revolutionary. This benefits industry players in two ways. First, it decreases regulatory risk because incremental improvements to existing devices can go through a streamlined review process at the FDA. Second, it reduces the odds that one company will leapfrog the rest by rolling out a truly revolutionary product. Although major advances in medical devices do occur, they're less common than in some other areas of health care, so industry players tend to compete by making each successive generation of any particular device just a little bit better than the previous one. (Contrast this type of competition with the winner-take-all structure of the drug industry, in which a new drug can literally wipe out the market for competing drugs in very short order.)

However, device firms are not without risk. Product cycles can be very short, so companies must spend heavily on research and development to keep up with their competitors. Especially in cardiac devices, where switching costs for surgeons are lower, market share among the major competitors can change dramatically within the space of 12 or 18 months as new products arrive on the