THE PHARMACEUTICAL INDUSTRY TODAY

Stan Finkelstein and Peter Temin
MIT

The pharmaceutical industry discovers, manufactures and sells brand-name and generic drugs. Brand-name corporations, such as Pfizer, Merck, and Novartis, invest in research and development to create new entities; they are known collectively as Big Pharma. Generic drug manufacturers, such as Mylan, Roxane, and Barr, generally produce drugs intended to compete with brand-name drugs after the patent of the brand-name drug has expired.\(^1\) Pharmacies and Prescription Benefit Managers (PBMs) convey drugs from manufacturers to consumers. Prescription drugs can only be obtained with a prescription from a health-care professional and include drugs such as Lipitor to treat high cholesterol and Zocor to treat acid reflux disease. Over-the-counter drugs (OTC drugs) do not require a prescription. OTC drugs are intended to treat self-diagnosed conditions (common cold, headache, etc.) where the threat of a drug being used incorrectly is low.\(^2\) An example of an OTC drug is the painkiller Advil (a brand-name containing the active ingredient ibuprofen).

The U. S. pharmaceutical industry currently employs 600,000 workers and has revenue of $250 billion. Profits are about $50 billion.\(^3\) This is about half of the world pharmaceutical market, as shown in Table 1. The EU accounts for another quarter, and the rest of the world, although growing rapidly, accounts for smaller shares. The top 20 pharmaceutical companies by sales are shown in Table 2. About half of these large firms are based in the U. S., reflecting the large American market share. This coincidence is less illuminating than it may appear, since all of these companies have sizable presences in the United States. If it were possible to allocate the activities of Big Pharma by country, the U. S. would contain a larger share of their activities.
The small share of even the largest companies in world pharmaceutical sales suggests a lack of market power. As we will show, this too is misleading.

Two aspects of the pharmaceutical industry are important. First, the industry and the U.S. government are closely entwined, and the industry – particularly since the 1960s – works diligently to develop and influence government rules on safety, efficacy, and marketing to its advantage. Lobbyists for the major drug companies are no strangers to the halls of power in Washington, and political contributions from the industry fuel elections from coast to coast. The fortunes of the pharmaceutical industry are tied closely to what government does, and the high earnings of drug companies make these investments in influence possible.

Second, the pharmaceutical industry – like most technologically active industries – is constantly in the process of reinventing itself. It is the most research-intensive industry in the United States, and news of drug discoveries and therapies are in the newspapers on an almost daily basis. We lack a metric to evaluate the speed of change, but it appears to have been very rapid in the decades following the Second World War. While it is dangerous to predict the future, we may be entering another period of rapid change today.

The U.S. government’s involvement with medications goes back to the 1906 Pure Food Act, but it was during the Great Depression that drug regulation began to make a significant mark. The New Deal philosophy that industries need regulation to operate well touched drug companies directly. In 1933, Congress saw a first draft of what eventually became the 1938 Pure Food and Drug Law, one of many so-called “Second New Deal” measures designed to lift the United States out of its economic woes.

German scientists researching dyestuffs found sulfanilamide, an antibiotic, more or less by accident. Aspirin had come about in much the same way many years earlier. But
sulfanilamide pills were unpalatable. So, in 1937, the U.S. pharmaceutical company, S.E. Massengill Co. introduced a liquid form, dissolving the drug in diethylene glycol – more commonly known as antifreeze.4

Like all non-narcotic drugs in 1938, sulfanilamide was available without a prescription; anyone could buy it. It didn’t matter whether you had a doctor’s prescription; you were free to self-medicate. And 100 people died from this toxin in one of the worst cases of adverse drug reactions in history. In the summer of 2007, people (and their pets) once again died from diethylene glycol, which Chinese producers used to make pet food and toothpaste.

Congress in 1938 didn’t want another sulfanilamide-like disaster, but the FDA lacked the authority to act. So Congress set out to make self-medication safer, stipulating that drugs be labeled either with an explanation about how they could be used safely or with some indication that they were safe to use “By Prescription Only.” It was up to the drug companies themselves to choose which label to use. The newly-empowered FDA interpreted the law to limit drug availability with “By Prescription Only” labels.

The FDA set up this category to be a transition between safe and unsafe drugs, presumably on the basis that it was hard to make an up-or-down decision in marginal cases. But the drug companies saw an opportunity. If they labeled drugs, “By Prescription Only,” they could sell drugs that would not be deemed safe for self-medication. The number of these drugs multiplied rapidly after the Second World War as modern antibiotics were introduced.

The pharmaceutical industry we know today owes its existence to the new antibiotics. Penicillin was the first and greatest. Isolated in 1929, it was made into a potent drug during World War II, and by war’s end had completely supplanted sulfa drugs as the treatment of choice for battle injuries. In 1944, some 19 U.S. companies produced penicillin; the largest five
accounted for nearly 90 percent of the total. Only one of these five was vertically integrated—that is, combined manufacturing, packaging, and sales of drugs.

After the war, as the business climate transformed into what became boom years, antibiotics were a very attractive business proposition for drug companies. In 1944, Selman Waxman of Rutgers University discovered streptomycin, and it wasn’t long after that scientists and drug companies realized that penicillin was just the beginning of a spate of antibiotic “wonder drugs.” It was a turning point for what has become one of the strongest and most profitable industries in U.S. history.

Waxman’s discovery was especially promising because his method—screening soil samples for the presence of agents that kept soil relatively harmless—could be generalized. It was icing on the cake when it turned out that streptomycin could be patented; even though the underlying antibiotic was natural, the patent office ruled the refinement and packaging of the drug had led to a “new composition of matter.” This meant companies using Waxman’s method could make other proprietary discoveries—and, of course, any new drugs resulting from the discoveries could be labeled “By Prescription Only” and marketed directly to doctors.

Prior to the war, nearly all drug companies had formulated medicines and furnished them in bulk to doctors and pharmacists. Under the new regulations, existing drug companies and new entrants jumped at the chance to build vertically integrated firms that would discover, produce, package, promote, and sell new drugs in finished form to doctors. As they integrated forward from manufacturing into marketing, new technologies encouraged them to integrate backwards into drug research and development. The modern pharmaceutical company as we know it dates from these early postwar years.
R&D spending grew, as did marketing. A race ensued to discover new drugs. Patents did their job, restricting competition and thus encouraging more innovation. Sometimes, companies combined to avoid patent fights. Business boomed. The share of prescription drugs in pharmacy sales rose from near 10 percent in 1940 to 40 percent a quarter-century later, and the proportion of drugs packaged in their final form by their actual manufacturers increased dramatically.

Meanwhile, direct advertising to doctors – called “detailing” – grew and intensified. Drug companies sent representatives – “detail men” – to visit doctors personally and urge them to use new drugs. They left behind the pens, pads of papers, magnets, and drug samples we’ve all seen at their offices. The main producers of new antibiotics spent more than half of their advertising dollars on detailing in the 1950s, and doctors received most of their information about new drugs from detail men.

The market power of the pharmaceutical industry was on the rise, as reflected by profits. But consumers, amazed at the new “wonder drugs,” didn’t seem to mind. After all, these drugs saved lives. They were cheap compared to a stay in the hospital. Some politicians in Washington, though, did begin to stir, upset at the high profits of the new, vertically integrated drug companies. In the early 1960s, Senator Estes Kefauver held a set of widely publicized hearings on the drug industry. His particular concern: “He who orders does not buy, and he who buys does not order.” This fact made the demand for drugs insensitive to price, since doctors didn’t care about the price and patients had no choice among prescription drugs. No wonder companies’ profits were high: even if prices rose, sales volume remained virtually constant.5

Kefauver introduced a bill to reduce the drug companies’ market power, but it was so diluted in committee that he refused to floor-manage his own bill. Then came another drug disaster. Thalidomide, an anti-nausea drug often used for pregnant women, produced phocomelia
in their children, that is, children born without hands or feet. This new drug disaster changed the political climate and propelled new legislation into law, just as happened with sulfanilamide in 1938. But rather than address Kefauver’s aim of curbing the market power of pharmaceutical companies, the 1962 Drug Amendments rewrote the standards for approving new drugs. In doing so, the new law cemented the intimate relationship between the government and the industry.

Before 1962, safety – the issue in both the sulfanilamide and thalidomide disasters – was the sole standard for drug approval. The 1962 law expanded the standard to include efficacy, the ability of the drug to produce a desired effect. This changed three important aspects of the relationship between pharmaceutical companies and the FDA: drugs would now be sold only if the FDA actively approved a company’s New Drug Application (NDA), instead of simply not objecting; the FDA had new authority over testing of new drugs, which had to be done in accord with its guidelines; and firms had to get FDA permission to initiate testing in humans. The 1962 law applied not just to new drugs, but also those already on the market, which had to be brought up to the new standards. Committees met throughout the 1960s to review all them, with the FDA authorized to remove from the market any that failed to measure up.6

The 1938 regulations had inserted doctors between consumers and their medicines; the 1962 amendments put the FDA between doctors and the drugs they prescribed. It wasn’t much longer before the FDA’s mark on the production and marketing of all drugs was evident. And the 1962 law also created the conditions for today’s blockbuster mentality. By making it easier for generic manufacturers to enter the market, the law showed pharmaceutical companies that they needed to maximize revenues while they still enjoyed patent protection.

The pharmaceutical industry settled into a two-tier configuration. Big Pharma, the largest companies, discover new drugs and introduce them under patent protection and with brand
names. Their monopoly on new drugs is protected by patents, and they earn substantial profits from them. Profits are concentrated in a few “blockbuster” drugs that sell massively, spreading the fixed cost of drug R&D over millions of pills. The large companies compete among themselves with vigorous advertising, but not by lowering drug prices. Generic producers make and market drugs whose patents have expired. There is comparatively free entry in this part of the industry, and little market power as a result. Advertising is minimal, and competition is largely by price. The companies in this lower tier are not household familiares.

As more drugs became available without patents and in competitive markets, Big Pharma introduced a new marketing approach to complement detailing. The pharmaceutical industry urged the FDA to allow direct-to-consumer (DTC) advertising, citing its “educational” benefits. Eli Lilly & Co. embarked on an aggressive advertising campaign for its arthritis drug, Oraflex. Spectacular sales resulted, but the FDA reprimanded Lilly for “misleading information” in its ads. In late 1989, the Prescription Drug Advertisement Coalition – 14 major pharmaceutical companies and representatives from ABC, CBS, and NBC – lobbied the FDA to allow the networks to run ads for four popular prescription drugs in a test market. At the same time, CBS and ABC broadcast Nicorette commercials that named the prescription drug. A public hearing on DTC advertising followed in 1995, where pharmaceutical and advertising representatives came out in force to press for a change in policy. In 1997, the FDA said that a drug’s name and the condition it treated could be included in advertisements without the need to disclose every risk (a policy finalized in 1999). Drug companies and broadcasters hailed the greater “consumer awareness” that would result.

Advertisements for prescription drugs skyrocketed. Pharmaceutical industry spending doubled to $2.5 billion between 1997 and 2000 and reached $4.2 billion by 2004. Prescription
drug advertising is now ubiquitous on television and in the print media. And consumers took the bait: a 1998 national survey revealed that, “33 percent of those who have seen such ads have spoken to their doctors about an advertised drug. Of those consumers, 28 percent asked for prescriptions – and 80 percent of such requests were granted.” Profits swelled: each dollar spent on ads produced an additional $4.20 in sales. The industry’s pressure on the FDA clearly paid off.9

The success of DTC in generating revenue for pharmaceutical companies is good news for an industry that is now suffering from a relative dearth of new products to sell. The number of drugs receiving final FDA approval has hit a stagnation point, and the industry is not quite sure what to do. There’s still a steady growth in the number of Investigational New Drug (IND) applications submitted to the FDA (reaching 2,374 in 2002); that’s the petition to the FDA to allow testing of a new drug in clinical trials. But approval of New Drug Applications (NDAs) – the request to market after clinical trials are completed – for New Molecular Entities (NMEs) has fallen from a peak of 53 in 1996 to only 17 in 2005.10

With such a low probability of launching a candidate molecule onto the market successfully, drug companies were concerned when researchers began to show a “dark side” to DTC – namely, that it manipulates the way patients think about medicines – soon after the ads began to run. The industry countered with contrary findings.11 Controversies over several drugs – and, ultimately, their recall – have widened the skepticism of the consumers targeted by DTC advertising. In October 2004, Merck recalled its arthritis drug Vioxx, which the company had been promoting aggressively with DTC advertising since 1998. Some two million people had Vioxx prescriptions. Only later was it discovered that COX-2 inhibitors such as Vioxx increase
the risk of heart attack and stroke in patients; an outstanding question is whether drug firms knew
this before their medicines hit the market. In April 2005, Pfizer pulled its similar drug, Bextra.

All this coming and going of new drugs raises the persistent question of pharmaceutical
profits. Big Pharma says its high profits are justified by the high risk the companies take, as
shown by the kind of troubles just described. But there is a great difference between risk at the
level of individual drugs and risk at the company level for large drug companies. The companies
are large enough to hedge their bets on many new drugs, and it is an open question whether they
can diversify their risk to offset the risk of individual drugs entirely.

Traditionally, drug manufacturers sold their products to a few wholesalers, who in turn
were the middlemen that sold to many small, independent retail pharmacies. The new model
involves a Pharmacy Benefit Manager (PBM) – a middleman between the drug companies and
individuals or insurers who pay for prescription medications. Studies done by the Federal Trade
Commission, Government Accounting Office, and others that find PBMs help expand access,
promote quality, and, most important, reduce the cost of prescription drugs to payers by upwards
of 27 percent.¹²

PBMs accomplish these putative savings in several ways. They leverage their size and the
number of people they represent to negotiate discounts as much as 18 percent for brand-name
drugs, and 47 percent for generic drugs, while still providing employers and their insurers with
formularies that include drugs in most therapeutic categories. PBMs also substitute generic drugs
for a brand-name drug when appropriate. And they are eligible for manufacturer rebates based on
their purchases, which can reduce drug spending by 3 to 9 percent. PBMs also cut costs with
their mail-service pharmacies for the insured, offering brand-name drugs at prices 27 percent
lower and generic drugs at prices at 53 percent lower than the average cash price at retail
The Medicare Modernization Act of 2003 stipulated that PBMs take a major role in the funded Medicare prescription drug benefit. The PBMs claim they can reduce Medicare drug costs by up to 30 percent.

All of these seemingly straightforward benefits mask another picture. In the words of well-known commentator Ben Stein, to be a PBM means making money “by denying benefits of various kinds, especially prescriptions, to patients and employees, thus supposedly saving money for employers and keeping a big chunk of that money for itself.” More and more employers and pharmacies believe that PBMs have shied away from their original role as middlemen, transforming into profit-hungry organizations focused more on their own gain than on lowering drug costs for their clients. In the course of this transformation, they have become tied more closely to the big pharmaceutical companies.

PBMs lack transparency, which fuels suspicion that the drug companies themselves benefit from PBMs. But how could the drug companies benefit when they discount their prices for their PBM buyers? PBMs have grown so big that they now have the power to manipulate a drug manufacturer’s market share by persuading health plans to choose a particular drug. In return, the manufacturer offers the health plan a rebate. Details of these rebates are not disclosed to the health plan, and the PBMs keep a large portion – up to 25 percent, on top of the fee PBMs collect from the health plans they serve.

The problems don’t end with the lack of transparency. There also appears to be an absence of competition. Three PBMs – Medco Health Solutions, Caremark Rx, and Express-Scripts Inc. – control 80 to 90 percent of the PBM market. Some observers accuse PBMs of profiting from the sale of drugs to their clients at a much higher price than they pay for them from manufacturers. And PBMs may receive special incentives from drug companies to promote
more expensive drugs. Just as a PBM may substitute a generic for a brand-name drug in its formulary, it can substitute a more expensive drug for a cheaper equivalent if the drug company provides enough of an incentive. Even with the discounted prices, the health plan would end up incurring a greater cost.\(^{18}\)

Medco Health Solutions, the nation’s largest PBM, paid Massachusetts $5.5 million to settle allegations that the company kept millions of dollars from drug company rebates rather than passing the money on to the state. When twenty states and the federal government combined to accuse Medco of violating consumer protection and mail fraud laws, it arranged a $29.3 million settlement agreement.\(^{19}\) These lawsuits raise the question whether PBMs do honest business. No wonder several state legislatures, including Maine, South Dakota, and the District of Columbia, have passed laws requiring greater PBM transparency through fiduciary and disclosure provisions. On another front, employers have formed coalitions to require their chosen PBMs to pass on 100 percent of rebates and discounts they get from manufacturers to member companies. And still other employers have brought their rebate management services in-house or developed worksite pharmacies. Some insurers have also gotten into the PBM business on their own behalf.\(^{20}\)

The mail-order aspect of PBMs is also controversial. IMS Health estimates that drugs ordered by mail, the fastest-growing sales channel for prescription drugs, now accounts for close to 20 percent of the total U.S. prescription drug market. Since mail-order pharmacies are highly automated and require little building space or staff, they have an edge over retail pharmacies. The PBMs can fill and mail a prescription for $2.50 – a fraction of what it would cost at a retail store.
These changes are contributing to the disappearance of the independent pharmacy, now nearly extinct from neighborhoods across the United States. Independent druggists sold a third of all prescription drugs in the early 1990s; today they sell half that amount. The big pharmacy chains have a lot to do with that, but mail order has doubled over the last decade, providing stiff competition for independent pharmacies. Several large pharmacy chains are fighting back by creating PBM branches of their own,\textsuperscript{21} but whether this will create sorely needed competition is no certainty.\textsuperscript{22}

The pharmaceutical therefore appears to be entering a period of rapid change. Drug research and development are changing due to new technologies, and drug marketing is changing due in part to new government programs. The pharmaceutical industry has been among the stars of the American economy for the last half-century. There is every prospect that it will continue to shine in years to come, earning high profits and introducing new medications. As before, the risks of the latter are likely to be used to justify the former. But if recent history is a guide to the near future, this is not a risky industry for its major components.
TABLE I

Worldwide Pharmaceutical Market By Geographic Region in 2004

<table>
<thead>
<tr>
<th>Geographic Region</th>
<th>2004 Sales (in billions)</th>
<th>Share</th>
</tr>
</thead>
<tbody>
<tr>
<td>World Pharma Market</td>
<td>$550</td>
<td>100%</td>
</tr>
<tr>
<td>North America (U.S. Canada)</td>
<td>$248</td>
<td>48%</td>
</tr>
<tr>
<td>European Union</td>
<td>$144</td>
<td>28%</td>
</tr>
<tr>
<td>Japan</td>
<td>$58</td>
<td>11%</td>
</tr>
<tr>
<td>Asia *</td>
<td>$40</td>
<td>8%</td>
</tr>
<tr>
<td>Latin America</td>
<td>$19</td>
<td>4%</td>
</tr>
<tr>
<td>Rest of Europe</td>
<td>$9</td>
<td>2%</td>
</tr>
</tbody>
</table>

* China sales in Asia were $8 billion with 35 percent growth

Source: Pharmaceutical Executive in May 2005 (IMS Health data)
http://wistechnology.com/article.php?id=1903
<table>
<thead>
<tr>
<th>Company/HQ</th>
<th>Pharma Sales * (in billions)</th>
<th>Share</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>World Pharma Market</strong></td>
<td>$550.0</td>
<td>100%</td>
</tr>
<tr>
<td>1) Pfizer (U.S.)</td>
<td>$46.1</td>
<td>8.4%</td>
</tr>
<tr>
<td>2) Sanofi-Aventis (Europe)</td>
<td>$31.8</td>
<td>5.8%</td>
</tr>
<tr>
<td>3) GlaxoSmithKline (Europe)</td>
<td>$31.4</td>
<td>5.7%</td>
</tr>
<tr>
<td>4) Johnson &amp; Johnson (U.S.)</td>
<td>$22.1</td>
<td>4.0%</td>
</tr>
<tr>
<td>5) Merck (U.S.)</td>
<td>$21.5</td>
<td>3.9%</td>
</tr>
<tr>
<td>6) AstraZeneca (Europe)</td>
<td>$21.4</td>
<td>3.9%</td>
</tr>
<tr>
<td>7) Novartis (Europe)</td>
<td>$18.5</td>
<td>3.4%</td>
</tr>
<tr>
<td>8) Roche (Europe)</td>
<td>$17.3</td>
<td>3.1%</td>
</tr>
<tr>
<td>9) Bristol-Myers Squibb (U.S.)</td>
<td>$15.5</td>
<td>2.8%</td>
</tr>
<tr>
<td>10) Wyeth (U.S.)</td>
<td>$14.0</td>
<td>2.5%</td>
</tr>
<tr>
<td>11) Abbott Labs (U.S.) **</td>
<td>$13.8</td>
<td>2.5%</td>
</tr>
<tr>
<td>12) Eli Lilly (U.S.) **</td>
<td>$13.1</td>
<td>2.4%</td>
</tr>
<tr>
<td>13) Amgen (U.S.)</td>
<td>$10.6</td>
<td>1.9%</td>
</tr>
<tr>
<td>14) Boehringer Ingelheim (Europe)</td>
<td>$8.7</td>
<td>1.6%</td>
</tr>
<tr>
<td>15) Takeda (Japan)</td>
<td>$8.3</td>
<td>1.5%</td>
</tr>
<tr>
<td>16) Astellas (Japan)</td>
<td>$6.9</td>
<td>1.3%</td>
</tr>
<tr>
<td>17) Schering-Plough (U.S.)</td>
<td>$6.4</td>
<td>1.2%</td>
</tr>
<tr>
<td>18) Schering (Europe)</td>
<td>$6.1</td>
<td>1.1%</td>
</tr>
<tr>
<td>19) Bayer (Europe)</td>
<td>$5.4</td>
<td>1.0%</td>
</tr>
<tr>
<td>20) Eisai (Japan)</td>
<td>$5.1</td>
<td>0.9%</td>
</tr>
<tr>
<td><strong>Total Top 20 Companies</strong></td>
<td><strong>$314.0</strong></td>
<td>57.1%</td>
</tr>
</tbody>
</table>

* Only pharmaceutical product sales
** Midwest-based companies

Source: Pharmaceutical Executive in May 2005 (IMS Health data)
http://wistechnology.com/article.php?id=1903
Notes

8 A 1996 notice in the Federal Register addresses some of the issues brought up by the hearing, specifically reiterating that the 1993 request for pre-approval was not a legal requirement and soliciting further information from interested parties.US FDA. 1996b. Direct-to-Consumer Promotion. Federal Register 61(94) (14 May), 24314.
14 Pharmaceutical Care Management Association, 2005, op. cit.
19 To ensure cooperation, Medco’s practices and dealings are monitored by an independent auditor. In return, the companies pay Medco a negotiated administrative fee. This model is expected to save roughly 6 percent, or $50 million a year, on the group’s annual drug costs of $800 million. Two Large Employer Coalitions Insist on Full Transparency in PBM Arrangements. AISHealth. 2005a. Drug Benefit News, February 11, 2005.
20 Touchpoint Health Plan and Dean Health Plan, two physician-owned insurers in Wisconsin, joined forces to create Navitus Health Solutions to manage prescription drug costs. Insuring a total of about 600,000 lives, Navitus
saved $3 million in its first two months through drug rebates, compared with $300,000 in the last year from their previous PBM. Mark Huetten, Navitus director of client services, believes that insurers can do better than PBMs when they manage their own formulary, although it does require commitment and resources. One main benefit to a company managing its own drug formulary is that it can focus more on generics and more appropriate drugs, while PBMs tend to pursue major brand-name drugs. See Edlin, 2004, op. cit: AISHealth. 2005b. Latest Maine PBM Ruling May Not Bode Well for Industry’s Case, Analysts Advise. Drug Benefit News, July 15, 2005: Seay, M. 2005. Regulating pharmacy benefit managers with transparency. Healthcare Financial Management 59:5, 18.

Walgreen’s Health Initiatives, the PBM branch of the major drug store, created its own program called Advantage 90, which offers 90-day prescriptions in the store at the same low cost of mail-order services. This program is now used by more than 150 employers. Walgreen’s has also tried to shun the companies that participate in mail order services, now refusing to fill prescriptions in Ohio, where Express Scripts is the mandatory mail service. Rite-Aid, with its 3,400 stores in 28 states, has recently created its own PBM. Similar to Walgreen’s PBM branch, Rite-Aid will also offer the 90-day refill program at all its pharmacies at the same price of mail order services. John Malley of the pharmacy benefit consulting practice at PriceWaterhouseCoopers believes that Rite-Aid’s entrance into the PBM market will stir up competition in the industry. He believes the 90-day in-store refills offer employers something different from the regular PBM services. CVS also has acquired Caremark in another combination of pharmacy and PBM. Edlin, ibid: Wojcik, 2005, op. cit.

Boyle, 2005, op. cit.