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Fundamentals of the Prescription Drug Market

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OVERVIEW — *This background paper is a primer on the prescription drug market. It provides information on the fundamentals of the pharmaceutical industry and various marketplace stakeholders, including manufacturers, retailers, consumers, regulators, researchers, and purchasers. This paper also examines the various ways the federal government interacts with the pharmaceutical market. Due to the breadth of material addressed, some complex issues and relationships are presented in broad conceptual terms without extensive technical detail.*

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Fundamentals of the Prescription Drug Market

For millions of Americans, prescription drugs save lives, ease suffering, reduce disability, and restore vitality. Vaccines have virtually eliminated the threat of horrible diseases, such as polio, diphtheria, and whooping cough, that once made childhood a more precarious time of life. Protease inhibitors can commute the death sentence that HIV infection once conferred; antipsychotic medications allow many mentally ill persons to live full, productive lives in their communities; and beta blockers can help prevent repeated heart attacks. These are only a few examples of the many medical “miracles” that have built the public’s faith in and expectations for pharmaceutical interventions.

The history of pharmaceuticals is replete with success stories, but prescription drug products and the miracles they enable come with a hefty price tag. In 2002, over \$160 billion was spent on prescription drugs in the United States, representing a fourfold increase since 1990.¹ Already high costs of prescription drugs continue to rise, alarming consumers, motivating private and public purchasers to establish aggressive cost control measures, and stimulating Congress to enact major policy changes. Although the importance of prescription drugs to modern medicine is well accepted, some critics question whether current spending levels and prescribing patterns are an efficient use of the already stretched health care dollar.

Though the factors driving the growth of prescription drug spending and the impact of such growth on coverage and access are a source of debate, few question the benefits of a robust, innovative pharmaceutical market. New pharmaceutical treatments and those in development offer hope to the sick and may ultimately reduce the burden of disease. Prescription drugs can facilitate cost-effective management of chronic illnesses and may potentially minimize “downstream” costs associated with hospitalizations and other health crises. Advances in science such as gene therapy, cell regeneration, therapeutic cloning, and the completion of the human genome sequencing provide hope for the prevention and treatment of disease in the future.

Policy efforts to influence the pharmaceutical market are complex and contentious, as with any high-stakes endeavor. The narrow passage of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003 and the continuing debate over the importation of prescription drugs reflect the strongly held—and often conflicting—views and interests of patients, providers, payers, manufacturers, researchers, regulators, and

investors. This paper does not attempt to mediate these interests or advocate for any of these perspectives; it is intended to provide a descriptive overview of the prescription drug market, examine the roles of the various parties that contribute to this market dynamic, and alert the reader to disputed issues.

MARKET DYNAMICS

Growth Trends

Although they account for a relatively small portion of total health spending, expenditures for prescription drugs are growing faster than any other major health care sector. Hospital and physician services represent the largest shares of total health care spending: 31 percent and 22 percent of total expenditures, respectively. Although spending on prescription drugs has been a distant third, accounting for 11 percent of total U.S. health care spending in 2002,² it grew by 15.3 percent in 2002—an increase that far outpaced spending increases in hospital (9.5 percent) and physician (7.7 percent) services.³ Analysts expect this trend to continue over the next 10 years.

Increases in both utilization and price contribute to the recent growth in prescription drug spending, although the relative contribution of each is unclear. Utilization increases have been attributed to a wide variety of factors, including the growth in the number of elderly persons, the introduction of new drug products, the marketing practices of manufacturers, and the increase in consumer awareness and empowerment. The rationale behind the large increase in prescription drug use is hotly debated, and conclusive evidence pinpointing the driving factors remains elusive. The extent to which price increases spur overall spending increases is also controversial. Many contend that the introduction of new drug products—often significantly more expensive than the products they replace—is at least partially responsible for the growth in prescription drug spending.

Regardless of the debates over causation, most experts believe that the growth of prescription drug costs will likely continue to surpass growth in other components of health care spending. However, the rate of that growth is expected to decelerate. These projections are largely based on beliefs that the market share of lower-priced generic drug products will increase, higher levels of consumer cost sharing will dampen utilization increases, and fewer new drugs will be introduced. Taken together, these factors will likely slow the growth in prescription drug spending in future years.⁴ This deceleration continues a recent trend. In 2003, U.S. prescription drug sales grew 11.5 percent to reach \$216.4 billion.⁵ Though 11.5 percent sales growth is considered strong, particularly in the 2003 economy, the declining growth trend is a cause for concern for investors (Table 1).

TABLE 1
U.S. Prescription Drug Sales
Growth Rate

| Year | Growth (%) |
|------|------------|
| 1999 | 18.8 |
| 2000 | 14.9 |
| 2001 | 16.9 |
| 2002 | 11.8 |
| 2003 | 11.5 |

Source: IMS Health, "U.S. Total Sales Growth, 1996-2000," available at www.imshealth.com/ims/portal/front/articleC/0,2777,6599_40054593_1004844,00.html; "IMS Reports 16.9 Percent Growth In 2001 U.S. Prescription Sales," available at www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_1003965,00.html; "IMS Reports 11.8% Dollar Growth in 2002 U.S. Prescription Sales," available at www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_41276589,00.html; "IMS Reports 11.5 Percent Dollar Growth in '03 U.S. Prescription Sales," available at www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_44771558,00.html

The prescription drug industry is highly profitable, although accurately measuring the industry's profitability is difficult. Responding to concerns about the magnitude of the industry's profit margins, industry representatives contend that standard accounting that measures current revenues relative to current costs does not adequately address the fact that revenues from drug research investments are not realized for many years. Regardless of measurement, however, it is accurate to say the U.S. prescription drug industry performs well relative to other U.S. industries.

Top Performers

Overall, the U.S. prescription drug market is relatively fragmented. Only five of the leading companies reported sales revenues in excess of 5 percent of the market. In 2003, the ten top-ranked companies in terms of sales had a combined market share of 59.6 percent,⁶ and all of them were large research-based manufacturers. The top eight rankings did not change from those of 2002 (Table 2).

Rankings of companies on the basis of prescription volume are a bit different. Three of the top ten companies—Watson, Mylan, and Teva, ranked number 3, 4, and 5, respectively—are generic firms. Generic products account for less than 10 percent of total sales for the U.S. prescription drug market⁷; however, they account for 51 percent of the total prescriptions filled.⁸

Major mergers between pharmaceutical companies have occurred at a rate of about one per year over the last 15 years.⁹ Pharmaceutical company mergers peaked in the early 1990s with six mergers occurring in 1994.¹⁰ Higher research and development costs are a factor cited for the trend in mergers and acquisitions. In recent years, merger activity in the industry has involved biotechnology companies. Research manufacturers increasingly turn to biotech companies to fill their research and development needs, sometimes by buying a biotech firm's entire pipeline of products. According to BIO, an association representing biotech companies, academic institutions, and state biotech centers, merger and acquisition activity rose 86 percent in 2003 compared with 2002. Despite this merger activity, the prescription drug market remains fragmented in aggregate.

Although by total sales and prescription volume the market is divided across many manufacturers, market share within therapeutic classes is a different matter. A therapeutic class represents a group of drug products that are similar in terms of chemical structure, clinical indications, pharmacology, or therapeutic activity.¹¹ Unlike many other product markets, in the prescription drug market there is little ability to shift consumer demand from one class of products to another. Consumers require a particular type of therapy and generally cannot substitute a different type of prescription drug product. In the food market, for example, consumers might be persuaded to buy less bread and eat more beef. But in the prescription drug

Generic products account for less than 10 percent of total sales for the U.S. prescription drug market but 51 percent of the total prescriptions filled.

market, antihistamines cannot substitute for antidepressants. For this reason, the competitiveness of the prescription drug market must be considered within the context of therapeutic class. It is also important to note that even within therapeutic classes, drugs may not be interchangeable. The true degree of competitiveness within a therapeutic class is highly contingent on the clinical indications for, the pharmacology of, the side effects related to, and other characteristics of the particular drugs within that class.

Market dominance by a single company within a given therapeutic class is not uncommon. Patent laws provide a market advantage to manufacturers of new drugs by precluding competitors from selling that specific product until the patents expire. As a result, brand name products typically drive expenditures within therapeutic classes. Although competition can occur between branded products within a therapeutic class, competitive forces are perhaps most robust when generic equivalents for a particular branded product are available.

Cholesterol-lowering drugs were the top-selling therapeutic class in 2003, with over \$13.9 billion in sales.¹² The cholesterol-lowering drug Lipitor, with \$6.8 billion in sales, has been the best selling prescription drug

TABLE 2
Ten Leading Corporations Ranked by Total U.S. Sales (in billions of dollars)
and U.S. Dispensed Prescriptions (in millions), 2003

| Corporation | | Total Sales (\$B) | Market Share (%) | Corporation | | Total Rx's (M) | Market Share (%) |
|-------------|-----------------------|-------------------|------------------|-------------|-------------------|----------------|------------------|
| 1 | Pfizer | 29.2 | 13.4 | 1 | Pfizer | 377.4 | 11.0 |
| 2 | GlaxoSmithKline | 18.6 | 8.5 | 2 | Novartis | 230.8 | 6.7 |
| 3 | Johnson & Johnson | 15.2 | 7.0 | 3 | Mylan Labs | 207.2 | 6.0 |
| 4 | Merck & Co. | 14.1 | 6.5 | 4 | Teva | 206.4 | 6.0 |
| 5 | AstraZeneca | 10.4 | 4.8 | 5 | Watson | 164.8 | 4.8 |
| 6 | Bristol-Meyers Squibb | 9.6 | 4.4 | 6 | GlaxoSmithKline | 159.6 | 4.6 |
| 7 | Novartis | 9.5 | 4.4 | 7 | Merck & Co. | 126.2 | 3.7 |
| 8 | Amgen | 7.7 | 3.6 | 8 | Johnson & Johnson | 104.8 | 3.0 |
| 9 | Wyeth | 7.6 | 3.5 | 9 | Abbott | 96.8 | 2.8 |
| 10 | Lilly | 7.5 | 3.5 | 10 | AstraZeneca | 91.8 | 2.7 |

Source: IMS Health, "Leading 20 Corporations by U.S. Sales, 2003," available at www.imshealth.com/ims/portal/front/articleC/0,2777,6599_42720942_44304255,00.html; and IMS Health, "Leading 20 Corporations by Total U.S. Dispensed Prescriptions, 2003," available at www.imshealth.com/ims/portal/front/articleC/0,2777,6599_42720951_43989649,00.html.

every year since 2001.¹³ Other top-selling drugs include the cholesterol drug Zocor (\$4.4 billion), the heartburn drug Prevacid (\$4 billion), the biotech anemia drug Procrit (\$3.3 billion), and the psychotherapeutic drug Zyprexa (\$3.2 billion).¹⁴ Lipitor was also the most dispensed product in 2003, with over 69 million filled prescriptions.¹⁵ Other leading products in terms of volume sold include the thyroid medicine Synthroid by Abbott (49.8 million prescriptions), the blood pressure drug Norvasc by Pfizer (36.4 million prescriptions), and the antidepressant Zoloft by Pfizer (32.7 million prescriptions).

Financial performance of individual manufacturers varies widely. For research-based manufacturers, financial performance is tied to the discovery of new products and the marketing of new and existing products. In contrast, financial performance for generic drug manufacturers is tied to the rapidity of market penetration and prescription sales volume.

Research and Development

Research is a critical element of success for pharmaceutical manufacturers. Research and development (R&D) that results in new products is essential for long-term revenue growth. A handful of innovator (that is, breakthrough) or branded drugs will provide the majority of a research manufacturer's revenues. The revenues from these products must pay not only for the investment costs of the successful products but for the ones that fail as well. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), only three out of every ten prescription drugs on the market generate revenues that meet or exceed average research and development costs.

In 2002, PhRMA member companies (including foreign-owned companies) invested \$32 billion in drug research and development—a 7.7% increase in R&D investment over 2001. R&D expenditures were 16 percent of total 2002 sales for these companies.¹⁶ According to PhRMA, the U.S. pharmaceutical industry invests a greater percentage of their sales in research than other American industries, including electronics, communications, and aerospace sectors.¹⁷

Discovering and developing new medicines is increasingly expensive and time-consuming. An increased focus on more complex diseases and the production of more sophisticated drug delivery systems increases the time needed for drug research and development. Furthermore, the complexity of clinical trials affiliated with the therapeutic classes researched extends the time and cost it takes to bring a product to market.¹⁸

According to the industry, it takes 12 to 15 years to discover and develop a new drug and bring it to market. Industry estimates that the direct cost of developing a new drug is approximately \$403 million (in year 2000 dollars). When capitalized, accounting for lost opportunity costs, the average "cost" of new drug innovation is approximately \$802 million (in

A handful of innovator drugs will provide the majority of a research manufacturer's revenues, which must pay for the investment costs of both the successful products and the ones that fail.

year 2000 dollars).¹⁹ If post-approval R&D costs such as the development of new formulations are included, industry sources argue that the true costs rise to \$897 million (in year 2000 dollars).²⁰

These estimates have been challenged extensively, however. Critics contend that industry estimates of research and development costs are grossly inflated. Many believe that these costs include activities that are actually marketing functions and that the estimates do not provide offsets for federal tax credits and other subsidies to support research and development costs.

Though the industry provides much of the intellectual and financial capital to develop products and bring them to market, the federal government also invests in drug development through intellectual property protection, federal support for research and development, and tax subsidies.²¹ These federal vehicles for supporting drug research and development are created to ensure patient access to new medical therapies, but they also are important to the finances of pharmaceutical companies.

■ **Patents and marketing exclusivity provisions** limit competition for a defined period of time, allowing brand name products to dominate the market and establish name recognition. The effective patent life for pharmaceutical products receiving U.S. Food and Drug Administration (FDA) approval is generally less than the 20 years provided by the U.S. Patent and Trademark Office because companies file for patents early in the development process. Opportunities for patent restoration and other marketing exclusivities are provided through a variety of federal acts, including the Hatch-Waxman Act, which provides up to five years of patent restoration; the Orphan Drug Act, which provides seven years of marketing exclusivity for products designated as “orphan drugs”²² by FDA; and the Food and Drug Administration Modernization Act, which provides six additional months of marketing exclusivity beyond patents or other exclusivities for companies performing pediatric studies approved by the FDA. These laws have had an impact on effective patent life for new drugs. According to one estimate, the effective patent life of drugs has increased from 8.1 years for drugs approved between 1980 and 1984 to 15.1 years for some drugs approved in the late 1990s.²³

■ **Federal government support for drug R&D** also includes financial support of biomedical research at the National Institutes of Health (NIH) and other research facilities. Federally funded research can result directly or indirectly in new pharmaceuticals. Much of the federally sponsored research is “basic” in nature without thought to specific drug therapies; however, it can lead to biological materials or lab processes that make it possible for the industry to pursue R&D that is directly relevant to new pharmaceuticals.²⁴ There are no recent estimates of how much NIH spends on drug R&D. A study by the former Congressional Office of Technology Assessment (OTA) estimated that in 1988 federal agencies spent about \$400 million on preclinical drug discovery, or 14 cents for

Industry provides much of the capital, but the federal government also invests in drug development through intellectual property protection, support for research, and tax subsidies.

every \$1 spent by industry on preclinical R&D. The OTA also found that federal agencies spent about \$200 billion on clinical R&D, or 11 cents for every \$1 spent by industry on clinical drug R&D.²⁵

■ Federal tax policy provides subsidies in the form of **tax credits for industry R&D**. The Research and Experimentation (R&E) Tax Credit, created in 1981 to encourage firms to increase R&D expenditures from year to year, covers all R&D necessary to obtain FDA approval to market a drug.²⁶ Other tax credits available to the pharmaceutical industry for R&D include the Orphan Drug tax credit—equal to 50 percent of qualified expenses for human clinical trials of drugs designated as orphan drugs—and the U.S. possessions tax credit, which provides tax credits to businesses that invest in U.S. possessions, such as Puerto Rico.²⁷

Research investment by U.S. pharmaceutical firms has climbed steadily over the last two decades; however, rising R&D spending has not resulted in increased development of new innovator products. The majority of new drug applications approved by FDA each year are for drugs that are modified versions of existing approved drugs, commonly referred to as “me too” or drugs. These types of drugs require less R&D investment and represent less commercial risk than the initial innovators in their therapeutic class. They also offer little in terms of new clinical benefit over their predecessors. Instead, their benefits can be found in fewer side effects, different dosage, or different delivery methods (for example, oral, injection, patch, etc.) than the innovator product. Their differences from the innovator products, however, are enough to qualify them as a new drug and therefore qualify for patents. As a result, “me too” drugs are often criticized for driving rising prescription drug costs, because they essentially extend patent protections and limit access of generic drugs to the market.

The annual number of new drugs receiving FDA approval that are considered to be marks of innovation—drugs that are different in structure from those already on the market, categorized as “new molecular entities” (NME)—is low. In 2002, only 17 were approved, the fewest number approved by FDA since 1983.²⁸ In 2003, 21 were approved in comparison to the high of 35 approved in 1999.²⁹ This lack of innovator productivity raises concerns about the impact of the industry’s R&D investment.

Several factors are believed to contribute to this return on research investment. Advances in basic science have significantly increased research opportunities. The number of drug targets—disease-specific proteins, receptors, enzymes and genes—has risen dramatically from 500 to more than 5000 in recent years, and there has been an expansion in research to investigate them. R&D might be becoming more expensive because the “low-hanging fruit” has already been picked and because areas of unmet medical need are in complex diseases difficult to understand and control.³⁰ This leads to longer development processes with more complicated clinical trials.

The majority of new drug applications approved by FDA are for drugs that are modified versions of existing drugs, known as “me too” drugs.

Changing industry structure may also affect industry productivity. Thirty years ago, most research affiliated with drug discovery was conducted “in house.” During the 1980s, the industry became more complex with the introduction of biotechnology companies. Biotech drugs differ from traditional chemical pharmaceuticals in key ways. Biotech medicines are synthetic versions of natural biologic substances (for example, proteins, enzymes, and antibodies) and are generally injected or infused directly into the bloodstream. Only a handful of traditional research-based manufacturers (also known as “Big Pharma”) actually research and develop biotech drugs. Instead, research manufacturers use agreements with biotech firms to keep their drug development pipelines robust. These agreements may be driving up the cost of drug development.

Contractual agreements and collaborative arrangements between manufacturers and biotech firms have been increasing. In 2003, the pharmaceutical industry struck more than 300 new deals with biotech companies to manufacture and market biotech’s drug products,³¹ and 21 new biotech products received FDA approval, including products for HIV, Alzheimer’s disease, cancer, psoriasis, and asthma. Sales for biotech drugs also grew 22 percent in 2003, with the global market for biotech drugs exceeding \$30 billion.³² Twenty-five to forty percent of industry sales are reported to come from drugs that originated in the biotech sector.³³

Regardless of the contributing factors, measuring industry productivity and the ultimate impact of R&D investment is difficult because the “pay-off” from such investment takes a long time to materialize. R&D in the current market contributes to new drug development far into the future. Therefore, the true impact of increased R&D spending in recent years may not be realized yet.

Marketing

To help offset revenue losses due to fewer new drug launches and generic entries, manufacturers try to maximize performance of existing brands. Product promotion is a critical element of this effort. In 2002, drug manufacturers spent over \$19 billion on total product promotion, including samples, brochures, drug detailing (in other words, sales people marketing drugs directly to doctors in their offices), and direct-to-consumer advertising (DTC) (Figure 1).³⁴

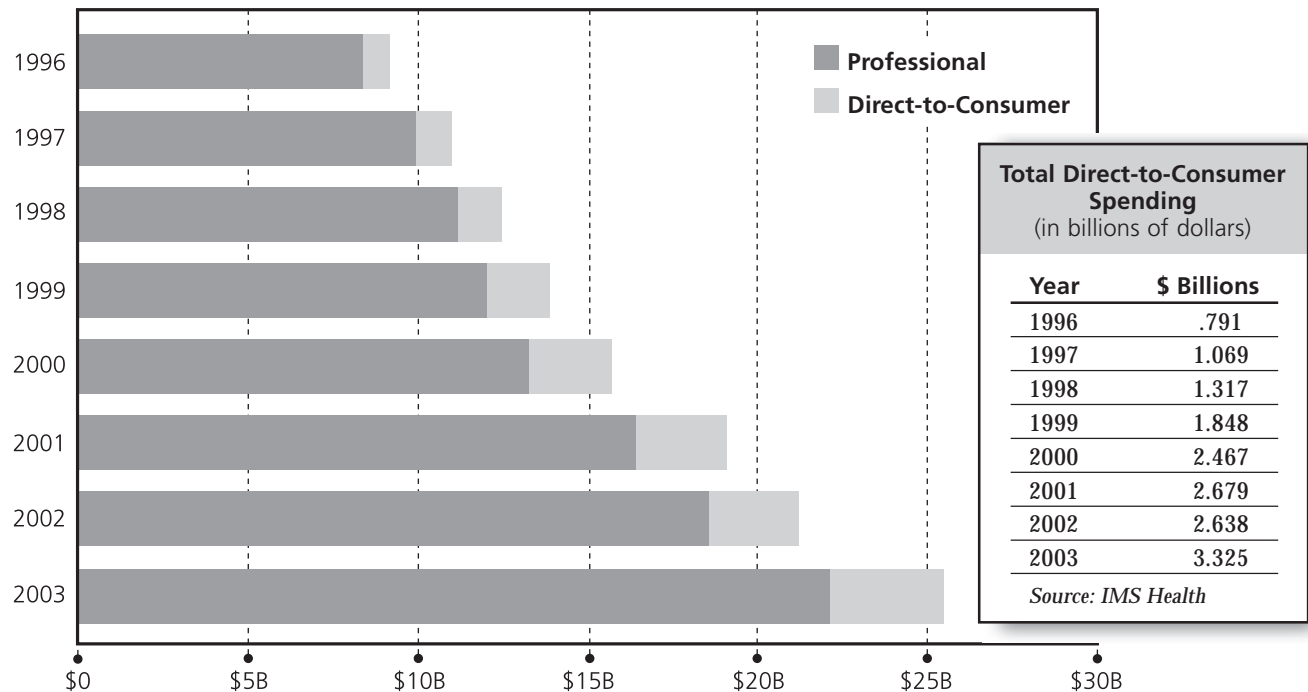
The bulk of all promotional spending is targeted toward physicians and other providers. Over 80 percent of all promotional spending can be categorized as “professional spending.” Professional promotional spending includes costs of journal advertisement, promotion and sales activities of drug representatives at hospitals and physician offices, and free drug samples. The retail value of free drug samples provided to physician’s offices reached almost \$12 billion in 2002, making it the largest component of professional promotional spending,³⁵ followed by physician office promotion at over \$5 billion. The dollar value of free product sampling grew faster than any other form of promotion in 2002.³⁶

Over 80 percent of all promotional spending can be categorized as “professional spending,” which includes journal advertisement, activities of drug representatives, and free drug samples.

Manufacturers are allocating a large portion of marketing resources to physician detailing; however, the traditional detail-based marketing model for professional promotion is being challenged. Increasingly, physicians use the Internet for medical information, including continuing medical education initiatives and point-of-care decision tools like electronic prescribing. Manufacturers are committing greater resources to “e-marketing.” Some market experts believe that point-of-care e-prescribing and related integrated drug reference tools are on the verge of becoming the most powerful marketing tools. Various estimates have projected that over 50 percent of physicians will adopt e-prescribing by 2005.³⁷

Although the overwhelming majority of promotional spending is geared toward providers, DTC spending is a subject of ongoing debate. DTC was the fastest growing component of all pharmaceutical promotional expenditures in the late 1990s. From 1996 to 2000, DTC spending—advertisements in magazines, newspapers, and on television, radio and the Internet—tripled (Figure 1, inset). Spending on television ads alone increased sevenfold.

FIGURE 1
Total Promotional Spending (in billions of dollars) in the United States by Type



Source: DTC promotion represents the expenditures for direct-to-consumer pharmaceutical advertising for prescription products on television, in magazines and newspapers, on radio, and outdoors. Professional promotional spending includes costs for sales activities, including product samples, office- and hospital-based physicians and directors of pharmacies, and advertising expenditures for prescription products appearing in medical journals. IMS Health, “Total U.S. Promotional Spend by Type, 2003” and “Total U.S. Professional Promotional Spend by Type,” available at www.imshealth.com/ims/portal/front/articleC/0,2777,6599_44304752_44889690,00.html.

Some believe the surge in DTC spending is linked to the relaxing of FDA rules on mass media advertising for prescription drugs, which occurred in 1997. However, others point out that the increase in spending started before 1997 and therefore the new guidelines may not be the sole reason for the increase.³⁸

DTC advertising is concentrated on a few products in a variety of therapeutic classes. According to IMS Health, the top DTC-promoted brands in 2001 were the anti-inflammatory drug Vioxx by Merck & Co (\$135 million), the arthritis drug Celebrex by Pfizer (\$130 million), the heartburn medicine Nexium by AstraZeneca (\$127 million), the erectile dysfunction therapy Viagra by Pfizer (\$101 million), and the allergy medicine Allegra by Aventis (\$90 million). In general, top-selling products have large DTC expenditures, although the products with the most promotional expenditures do not always correspond to the top-selling products.

Manufacturers tend to spend the most on consumer ads for drugs used to treat chronic conditions that require treatment over extended periods of time such as asthma, depression, allergies, arthritis, and diabetes. Drugs with low occurrence of mild side effects are also better candidates because there is less information on risk that needs to be conveyed to the consumer. DTC advertising for certain types of drugs such as “lifestyle” drugs (for example, Viagra) is viewed as a good investment because insurance usually does not cover such products, leaving most consumers to pay for them completely out-of-pocket. Within a specific class of drugs, the intensity of DTC advertising varies, and the amount of advertising for specific products changes over time.³⁹

Critics argue that DTC advertising drives spending as well as inappropriate utilization and takes money away from R&D. They claim DTC advertising leads consumers to seek drugs when other treatments may be more appropriate or to seek newer, more expensive drugs that may (or may not) be as effective as their predecessors.

Supporters argue that DTC advertising educates consumers about treatment options and that increased drug utilization encouraged by DTC has improved public health.⁴⁰ Furthermore, they argue that it prompts patients to seek medical advice about health concerns, resulting in new diagnoses and additional health care recommendations.

The U.S. General Accounting Office [(GAO), renamed the U.S. Government Accountability Office in July 2004] concluded in a 2002 study on DTC advertising that it appears to increase prescription drug spending and utilization. The GAO also found that spending on heavily advertised drugs increased faster than other sales and that this was due to an increase in utilization, not increasing prices. It also noted, however, that the spur in utilization may be due to the type of drug that is heavily advertised, namely the chronic condition drugs. Another fact to consider is that many of the same drugs promoted through DTC advertising are also promoted to physicians through drug detailing; therefore, determining the true influence of DTC is difficult.

The GAO found that spending on heavily advertised drugs increased faster than other sales and that this was due to increased utilization, not increasing prices.

Growth of Generic Drugs

Despite the efforts of research-based firms to fend off the advances of generic products, generic drugs are a growing component of the pharmaceutical industry with a steady increase in share of total prescriptions. When Congress passed the Drug Price Competition and Patent Term Restoration Act in 1984 (also known as the Hatch-Waxman Act) to streamline the approval process for generic drugs and increase their access to the market, generic drugs accounted for only 18 percent of the prescriptions filled. By 2003, generic products accounted for 51 percent of all prescriptions filled.⁴¹ Between 2002 and 2003 alone, generic sales grew by 22 percent and the volume of generic prescriptions grew by 9.2 percent.⁴² These levels represent new highs in both dollars spent on and prescriptions for generic drugs.

Generic drug manufacturers do not have to conduct clinical trials and prove safety and efficacy the way brand name drug manufacturers do for a new patented drug. Instead, they have to prove “bioequivalence,” which in general terms means their product must deliver the same active ingredient in the same dosage and in the same time frame as the innovator or brand product.⁴³ The cost for proving bioequivalence is about \$1 million, significantly less than the cost to develop a new drug.⁴⁴

The lower R&D costs of generics allow drug manufacturers to price generics aggressively, usually at about a third of the price of brand name products. This translates into significant savings for consumers and purchasers. According to the Generic Pharmaceutical Association, the average price per prescription for a brand name drug is \$84.21, whereas the average price for a generic drug is \$30.56.

According to the FDA, brand name firms are involved with the production of approximately 50 percent of generic drugs. Creators of patented products sometimes manufacture the generic versions, and sometimes they also use licensing agreements with generic manufacturers for the production of generic versions of their patented drugs. Some of these agreements have been criticized as financial arrangements intended only to delay the production and distribution of generic substitutes.

Patent expirations for brand name drugs are one of the driving forces behind rising generic drug sales. The expiration of patents for top-selling brand name drugs creates market opportunities for generic drugs. In year 2005 alone, several major branded drugs that collectively represent over \$13 billion in sales (in year 2003 dollars) will lose patent protection (Table 3).

Pravachol and Zocor are top-selling cholesterol medications, and Zoloft is a leader in the antidepressant category. The loss of patent protection for these products will likely have a major impact on the overall expenditures in these therapeutic classes.

Payer cost-containment trends are another driving force behind the growing market share of generics. Generic substitution requirements in

In 2003, generic sales grew by 22 percent and the volume of generic prescriptions grew by 9.2 percent, representing new highs for the generic drug market.

TABLE 3
Patent Expiration Dates for Five Top-Selling Prescription Drugs
(in billions of dollars)

| Drug Name (Manufacturer) | 2003 Sales (\$B) | Date |
|---|-------------------------|---------------|
| Prevacid (TAP Pharmaceuticals) | 4.0 | July 2005 |
| Pravachol (Bristol Myers Squibb) | 2.0 | October 2005 |
| Zocor (Merck & Co.) | 4.4 | December 2005 |
| Zoloft (Pfizer) | 2.9 | December 2005 |

Source: Sales data from IMS Health, "Leading 20 Products by U.S. Sales, 2003," available at www.imshealth.com/ims/portal/front/articleC/0,2777,6599_42720942_44304277,00.html; patent expiration dates from the Generic Pharmaceutical Association, "Drug Patent Expiration List 2002 - 2006," available at www.medvantx.com/550.asp?nav=500.

Medicaid programs and multitiered copays in private health plans effectively reduce cost while helping to accelerate the conversion from brand name to generic products. Years ago, it would take over six months for a generic product to capture 50 percent of the dispensed market; in the current market, it can happen in as little as six to eight weeks.⁴⁵

Though generic drugs are gaining ground in the U.S. pharmaceutical market, barriers to entry remain. Patent extensions, restorations, and periods of market exclusivity granted to brand name manufacturers can delay when generics are able to enter the market. Patent challenges by brand name manufacturers also impose legal fees, delaying generic approvals and thus market entry. Product management strategies by brand name manufacturers, such as product oversampling to physicians, aggressive DTC marketing, and other strategies, can delay market penetration and affect the rate of conversion from brand name to generic. For example, ulcer medications and antidepressant drugs, the second- and third-ranked therapeutic classes by U.S. prescription sales for 2002, maintained their sales rankings in 2003 even though both classes have generic substitutes available and there is an over-the-counter ulcer medication available.

The MMA contains provisions to close unintentional loopholes in the Hatch-Waxman law that delayed the marketing of generic drugs. Among its provisions, MMA allows brand name manufacturers filing patent infringement litigation against generic drug manufacturers only one 30-month stay of marketing exclusivity. Previously allowed were multiple stays, which could be overlapping and consecutive and could delay generic drug market entry for years. The limitation imposed in the new law is contentious and will continue to generate policy discussion.

Access to the lucrative biotech market is currently not available to generic manufacturers. When the Hatch-Waxman Act was passed in 1984, the biotech industry was in its beginning stages and none of its drugs had been approved yet. As a result, Hatch-Waxman provides no guidance to the FDA regarding approval for generic versions of biotech products. Unlike chemical medicines, biologics cannot be tested for bioequivalency; new tests must be developed to determine whether a generic version of a brand name biologic offers the same therapeutic effect.

Biotech drugs are among the most expensive drugs to develop and are priced accordingly. As patent expirations for the initial products of the 25-year-old biotech industry approach [reportedly 17 biotech drugs worth more than \$10 billion in sales (in year 2000 dollars) will lose patent protection in 2006], the industry, Congress, and the FDA are beginning to debate whether generic biologics should be allowed and what the approval process should require.

The research-based pharmaceutical industry argues that making biologics is still so complex that generic firms should have to prove safety and effectiveness as if they were creating a new medicine. The FDA is in the process of putting together scientific guidelines on how to prove that copies of biologics are similar to the original medicines, but it has cautioned in the past that there are significant scientific issues about how to show “sameness” to assure the agency that generics are safe, pure, and potent, as well as equivalent to the brand.

A Complicated Marketplace

The marketplace that links consumers to manufacturers is highly complex and involves a number of intermediaries. The “sell” side of the prescription drug transaction includes manufacturers who produce the product, as well as wholesalers and retail distributors who buy the product and resell it to the consumer. On the “buy” side of the transaction, the consumer is actually an amalgamation of multiple parties including (a) the patient who will use the product and will likely pay for at least a portion of the purchase price, (b) the physician, or other health care provider, who prescribes the drug, and (c) the insurer (if the patient has prescription drug coverage) who shares the financial burden of the purchase with the consumer, may negotiate prices with retailers and the manufacturer, and can play a role in limiting or shaping product options.

Individuals — According to surveys by the Kaiser Family Foundation⁴⁶ over half (54 percent) of Americans say they take prescription drugs on a regular basis, and one-fourth (24 percent) say they take three or more drugs regularly. Thirty percent say they currently have more than five prescription drugs in their medicine cabinet.

Unlike most consumer products, users of prescription drugs have limited choice in selecting a particular product. Purchases must be initiated by

As biotech patent expirations approach, the industry, Congress, and the FDA are beginning to debate whether generic biologics should be allowed and what the approval process should require.

physicians or other appropriate health care providers via prescription of a particular drug. Patients generally lack the clinical expertise necessary to influence providers' prescribing choices, although the aim of DTC advertising is clearly to motivate patients in this regard. Despite the increase in DTC advertising, most manufacturer marketing focuses on physicians in recognition of the role they play in product selection.

Insurers — Insurance coverage also directly affects access to prescription drugs. The Kaiser survey found that 25 percent of respondents did not have prescription drug coverage, and 29 percent said they have not filled a prescription because of the cost. Insurers can also influence the types of drugs used by an individual. In general, consumers with drug insurance use more prescriptions, including more brand name drugs, and have greater prescription expense than people without insurance. A driving force of this dichotomy is the price insulation that third party coverage provides—particularly for higher-priced brand name drugs. Faced with a flat copayment instead of a retail price, people with drug insurance are less sensitive to price differentials between drug products.

Third party payment (public and private) continues to steadily offset the consumer's out-of-pocket share of drug spending. In 1994, out-of-pocket and third party shares of total drug expenditures were nearly equal. By 2002, the consumer out-of-pocket share was down to 30 percent.⁴⁷ The rise in third party payment over the years is due to an expanding share of total expenditures paid by private insurers, which reflects an expansion in drug coverage. In 2002, private third party payers paid \$77.6 billion for prescription drugs.⁴⁸

Out-of-pocket spending for prescription drugs, however, is growing at a faster rate than private health insurance spending.⁴⁹ A driving factor for this trend is the cost-containment measures imposed by third party payers, most notably managed care plans and their pharmacy benefit managers (PBMs).⁵⁰ PBMs are private firms that manage drug benefit programs for employers, insurers, and managed care plans. PBMs perform a variety of functions, including formulary design and management, pharmacy network and payment administration, mail order, rebate negotiations or management, and patient compliance programs.

Prescription drug formularies were introduced by health plans to influence prescribing patterns with the goal of reducing costs. Drugs on the formulary are covered, whereas nonformulary drugs are not. In recent years, fairly inclusive formularies with multitiered copayment levels have become the general rule in the administration of drug coverage. Such formularies create lower copayments for generic drugs and feature less expensive or more effective brand name products on a preferred drug list (PDL). Manufacturers are often willing to offer discounted prices in exchange for the guaranteed market share likely to result from inclusion in the PDL. The different copayment levels create incentives for beneficiaries to use generic or low-cost brand name drugs. This approach

Out-of-pocket spending for prescription drugs is growing at a faster rate than private health insurance spending.

provides coverage for a broad range of drugs, but shifts more of the expense for certain products (such as high-cost brand name drugs) to consumers. For most consumers, these copays and formularies affect them when they present their prescription to a pharmacist at a retail pharmacy.

Retailers — According to the National Association of Chain Drug Stores, there are over 35,000 chain drug store pharmacies (for example, CVS), mass merchandiser pharmacies (such as Target), and supermarket pharmacies nationwide. In addition, there are over 20,000 independent pharmacies that are small, privately owned individual pharmacies or small chain pharmacies.

In recent years, the distribution market has shifted away from independent, privately owned pharmacies toward chain drug stores, food stores, and mass merchandisers. These retail pharmacies dominate the distribution market, dispensing approximately 60 percent of all prescription drugs in the United States.⁵¹

Mail order service is a fast-growing segment of the distribution market. Mail order sales grew by 15.5 percent in 2003, resulting in a 13.2 percent market share.⁵² Lower copayments for mail order services offered by managed care organizations and PBMs are a driving force behind the growth in mail order purchases.

The Internet has expanded consumer access to prescription drugs. “Internet pharmacies” mimic traditional retail pharmacies in terms of products and services and compete directly with them; they dispense a similar line or range of drugs to consumers and may offer patient education and/or drug interaction screenings. There also are Internet “prescription sites” that offer access to a limited selection of drugs. Lifestyle drugs are promoted this way. Prescription order writing and filling services are provided at these sites. Finally, traditional retail pharmacies provide Internet sites as an option for consumers to place their refill and prescription orders.

Internet access to prescription drugs appears to provide convenience and easy availability; however, such pharmacy outlets raise significant safety concerns, regarding, in particular, patient education and safeguards, the monitoring of prescription writing, and the quality of the drugs themselves.⁵³ Internet pharmacies have already been implicated in scandals involving counterfeit and contaminated drugs.

Wholesalers — The majority of pharmaceutical drugs sold in the United States are purchased through drug wholesalers. Wholesalers provide a cost effective means for manufacturers and retailers to purchase, deliver, and sell prescription drugs. Serving as a middleman, wholesalers help lower manufacturers’ costs through large volume purchases while providing “one-stop shopping” for retailers, thus eliminating the need to negotiate contracts with individual manufacturers.

Chain drug stores, food stores, and mass merchandisers (such as Target) dispense about 60 percent of all prescription drugs in the United States.

Wholesalers generate revenue from both manufacturers and retailers. Retailers pay fees for distribution services, and manufacturers provide cash rebates and discounts for prompt or early payment. Wholesalers operate on narrow profit margins; the wholesale markup is modest, usually just a few cents for every dollar of prescription drugs sold. The average wholesale price (AWP) is intended to represent the average price at which wholesalers sell drugs to physicians, pharmacies, and other customers.

These “sticker prices” or “list prices” are commercially published and sold to public and private purchasers. They serve as a reference price for purchasers, with payments usually corresponding to AWP, less a specified percentage (for example, AWP minus 15 percent). AWP, however, is not an accurate reflection of actual market prices because it does not include discounts available to various purchasers. It is generally considered to be an overstated price and is facetiously referred to as “ain’t what’s paid.”⁵⁴

The recently enacted MMA addressed the problem of AWP by replacing it with the average sales price (ASP) as the basis for prescription drug reimbursement under Medicare Part B. The ASP is the average of a drug’s final sales prices in the United States, net of rebates or other discounts. The new payment basis will be implemented in 2005.

The wholesale industry is highly concentrated, with 90 percent of all sales made by only three companies. The “Big Three” are McKesson HBOC, Inc; Cardinal Health, Inc.; and AmeriSource Corp. As the principal pipeline of drug distribution, these large wholesalers purchase a full line of pharmaceutical products from manufacturers and resell them to retailers. In some cases, the products are warehoused by the large wholesaler then resold and distributed directly to retailers. In other cases, these wholesalers provide “brokerage services,” which can include delivery directly from the manufacturers without warehousing as well as allowing retailers and manufacturers to submit orders and payments through the wholesaler without involving the wholesaler in the delivery of the purchase.⁵⁵

Regional wholesalers deal with a smaller volume of drugs than the Big Three, but they sell to the same purchasers and compete with the large wholesalers. Small wholesalers vary in their size, product lines, and services. Some provide a full line of drug products, others provide only certain products such as injectables, and yet others team with medical supply companies to provide combination products of drugs and medical devices.

There also are secondary wholesalers who specialize in the purchasing and selling of select discounted pharmaceutical products to other wholesalers. The sources for these discounted products can be manufacturers offering sales to clear their inventory or meet sales quarter goals, and pharmacies and other wholesalers with overstocks. A distinguishing feature of secondary wholesalers is their willingness to risk capital by buying discounted products for quick resale. Secondary wholesalers compete entirely on price. Purchasing prescription drugs from secondary

The wholesale industry is highly concentrated, with 90 percent of all sales made by only three companies.

wholesalers is attractive to large and regional wholesalers because their discounted prices can undercut the regular contract price offered by the manufacturer. As a result, large and regional wholesalers may reduce contract purchases with manufacturers for certain drugs so they can take advantage of the secondary market sales.

The secondary wholesale market generates concerns regarding product safety, integrity, and pricing practices. There is no formal definition or count of secondary wholesalers, and regulation of the entire wholesale industry varies from state to state. Corrupt secondary wholesalers have been the root of several large counterfeit drug cases (for example, fake Lipitor) and “drug diversion” schemes—a sales practice that sends lower-cost drugs intended for institutional settings to retail settings—to make a profit. States have responded by tightening licensing requirements for wholesale businesses, and FDA is pursuing product packaging and tracking changes to ensure product safety.

FEDERAL GOVERNMENT

As might be expected for such an unwieldy segment of the U.S. economy, the federal government is a unique stakeholder in the pharmaceutical marketplace. It plays three distinct roles; as regulator, researcher, and purchaser, the government is an influential participant in the industry.

Regulation

The pharmaceutical industry is one of the most regulated industries in the United States, and the FDA is the federal agency responsible for overseeing the pharmaceutical industry.

FDA oversight of new prescription drugs can be classified into preapproval and postapproval activities. Preapproval activities focus on ensuring that a drug is safe and effective before it is marketed to consumers. Postapproval activities include postmarketing surveillance to ensure the ongoing safety of marketed drugs, the enforcement of good manufacturing practices so that drugs are manufactured in a consistent and controlled manner, and the monitoring of prescription drug advertising to ensure the truthful presentation of information regarding effectiveness, side effects, and so forth.

FDA is also responsible for overseeing the generic and over-the-counter (OTC) drug development, as well as marketing.

New Drugs — Regulatory authority for the agency is provided in the Food, Drug and Cosmetic Act (FD&C Act), which was passed in 1938. United States drug law has evolved dramatically since then, with the most significant change occurring with the Kefauver-Harris Drug Amendments of 1962. The Amendments fundamentally restructured the way in which FDA regulated new medicines, transforming a system of premarket notification into one that requires individual premarket approval

As regulator, researcher, and purchaser, the government is an influential participant in the pharmaceutical industry.

of the safety and effectiveness of every new drug.⁵⁶ Some believe that with passage of this legislation the regulation of drugs became the single most controversial (and perhaps the most important) of FDA's activities.⁵⁷

According to the FDA, no drug is absolutely "safe," and therefore the agency follows a "risk-based approach" for new drug approval. When a proposed drug's benefits outweigh its known risks, the FDA considers the drug safe enough to approve.⁵⁸

In general, the new drug development process starts with the discovery of NMEs, which are compounds that have not been previously approved by the FDA. Preclinical testing is performed on animals to determine safety and biological activity. The drug's sponsor, usually the manufacturer, eventually pursues an investigational new drug (IND) application from the FDA, which allows the sponsor to conduct human studies.

Controlled clinical trials (that is, human studies) are designed to assess the safety and efficacy of a drug for its proposed use. Clinical trials provide the only legal basis for demonstrating a drug's effectiveness.⁵⁹ Clinical trials are conducted in a three-phase process. Each phase requires larger patient populations and greater scrutiny of the drug's performance.

Phase I clinical trials typically involve healthy subjects and are designed to test a compound for metabolic properties, safety, and tolerance. Phase II trials involve selected populations with the disease or condition to be treated, diagnosed, or prevented and are designed to obtain information on safety and initial data on efficacy. Phase III trials are large-scale trials involving subjects with the target disease or condition and are designed to gather data on efficacy, safety, and drug-related adverse effects. Throughout the process, many potential new therapies fall by the wayside: Approximately 70 percent of drugs entering clinical trials complete Phase I, 33 percent complete Phase II, and 27 percent complete phase III.⁶⁰

Once clinical testing is completed, the drug's sponsor submits a New Drug Application (NDA), which is the basis for FDA approval. The NDA tells the drug's whole story, including what happened during clinical trials, what is included in its components and constitution, how the drug performed in animal studies, how the drug behaves in the human body, and lastly how it would be manufactured, processed, and packaged.⁶¹

New drugs typically qualify for 20 years of patent protection. This protection precludes competitors from marketing products with the same active ingredients. The "clock" for patents begins with the submission of the IND. Therefore, clinical testing and FDA review and approval time can consume a large portion of a drug's patent life, although some of this lost protection can be restored.

The amount of time it takes the FDA to review a new drug application has been reduced. The Prescription Drug User Fee Act (PDUFA) of 1992

No drug is absolutely "safe"; the FDA approves a proposed new drug when its benefits outweigh its known risks.

provided the FDA with a series of fees (for example, application fees, establishment fees, product fees, etc.) to hire additional staff to help quicken the NDA review process. As a result of the PDUFA and its reauthorizations in 1997 and 2002, the FDA is currently reviewing more than 90 percent of priority drug applications in 6 months or less and standard drug applications in 12 months or less.⁶² Before the passage of the PDUFA, NDA review took upward of 18 months.⁶³ According to PhRMA, this reduction in review time largely eliminated the lag time to approval that had existed between the United States and other industrialized countries.

The FDA has “fast track” policies and procedures in place to help qualified applicants navigate the NDA submission and review process. FDA staff work closely with applicants throughout the process to reduce potential delays in application submission and review. Products eligible for fast track designation address an unmet medical need.

The FDA has taken additional steps to make urgently needed drugs—namely drugs promising significant benefit over existing therapy to treat serious or life-threatening diseases—available sooner. Under the “accelerated approval” rule, FDA is allowed to approve a drug on the basis of a “surrogate endpoint,” which is a positive effect on a marker of the disease rather than an actual positive effect on survival of an illness.⁶⁴

FDA also allows broader use of investigational drugs prior to market approval. “Treatment INDs” and the “parallel track mechanism” for AIDS and HIV-related drugs allow promising drugs not yet approved to be used in expanded access protocols. This means individuals not qualifying to participate in the controlled clinical trials may be able to enroll in special protocols that allow them access to the drugs and provide manufacturers with additional information.

Generic Drugs — Regulation of generic drugs was dramatically reformed with a complex law called The Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act. This law amended the FD&C Act and various federal statutes that govern U.S. patents. It basically established the framework for the approval of generic drugs and their entry into the marketplace.

The Hatch-Waxman Act permits generic manufacturers to use and reference the safety and effectiveness research conducted by the brand name company when seeking FDA approval to market a copy of a brand name drug. Before 1984, generic manufacturers were required to duplicate this research. The law requires generic manufacturers to prove that their copies of the brand drugs they seek to market are chemically and biologically equivalent to the original drug. Generic manufacturers are permitted to begin testing of their drugs before the patent on the innovator drug expires, and brand name manufacturers must share relevant data with generic companies so such tests can be performed.

Under this law, the first generic company to file an abbreviated new drug application (ANDA) with the FDA for a copy of a patented drug gets 180

The FDA has taken steps to make urgently needed drugs—those promising significant benefit over existing treatments for serious diseases—available sooner.

days of “exclusivity,” meaning no other generic copy of that drug can come to market in that period. Finally, generic companies are required to “certify” to the FDA how their products will or will not infringe all existing patents on the drug they seek to copy.

The Hatch-Waxman Act also provides a vehicle for brand name companies to “restore” some of their product’s patent life lost during the testing and approval process. The maximum restored patent life is five years, and the maximum total effective patent life—meaning the time between FDA approval and a drug’s patent expiration after any restored patent life—cannot exceed 14 years. This lengthens a brand name drug’s protection from generic competition. The law also permits periods of “market exclusivity” for brand name products for new uses of a drug and for new active ingredients that have not been previously marketed.

Over-the-Counter Drugs — The FDA has a separate process for approving over-the-counter (OTC) products. Instead of reviewing and approving thousands of individual products, the FDA evaluates the active ingredients found in them. The FDA then publishes standards for specific OTC treatment categories (for example, antacids, laxatives, etc.). An OTC drug product does not need specific approval before marketing as long as the product meets its category standards.⁶⁵

Sometimes an approved prescription drug is deemed appropriate by FDA for self-use and the drug’s status is switched to OTC. To take this action, the FDA would determine that the drug treats a condition consumers can diagnose and manage themselves and, therefore, that the drug is sufficiently safe for use without prescriber supervision. The drug’s label must also explain potential adverse effects and conditions with clear direction.

Status switching from prescription to OTC is usually prompted by the drug manufacturer; however, other parties can petition FDA for OTC switches as well. This was the case with the top-selling allergy medicine Claritin. An insurance company initiated the process for an OTC switch for Claritin. Its motivation to pursue the switch was the savings that would result from the removal of Claritin from their formulary once it became available over the counter. The manufacturer, Schering-Plough, initially fought the petition because Claritin had a few years left on its patent. Shortly before Claritin’s patent expired, however, the manufacturer petitioned FDA for the OTC switch itself, which was granted. By getting an OTC version of Claritin on the market, the manufacturer was able to get a jump on the generic competition.

Research

The federal government is the largest supporter of academic-based research in life and health sciences⁶⁶ The National Institutes of Health (NIH) is the principal federal agency that funds and conducts biomedical research, including research on drugs.⁶⁷ In fiscal year 2003, the NIH’s budget was over \$27 billion.⁶⁸

The federal government is the largest supporter of academic-based research in life and health sciences.

Technology transfer is basically the “sharing and dissemination of scientific knowledge between researchers and research organizations and those who make practical use of the information including physicians, health care providers, and industry.”⁶⁹ According to the GAO, “much of the pharmaceutical related technology transfer between the public and private sector originates with research conducted by or funded by the NIH.”⁷⁰ The transfer of technology from government-based medical research laboratories to the private sector is an effort to have new pharmaceuticals brought to market more efficiently than would be possible for the federal agency acting alone.

In general, government and academic scientists conduct basic research identifying compounds, methods, and chemical reactions that may be of value in treating disease. Both the NIH and academic institutions conduct preclinical and clinical testing (that is, Phase I and Phase II clinical trials). In general, industry conducts the Phase III clinical trials and pursues approval for marketing.

Public-Private Partnerships — The key component of successful public-private technology transfer is the incentive to develop and commercialize government-owned research or inventions. Historically, the government generally retained the title to any inventions created under federal research grants and contracts. In 1980, however, Congress enacted two laws focusing on encouraging the commercialization of government-developed and -funded technologies:

■ **The Stevenson-Wydler Technology Innovation Act** addressed government-owned technology. It declared that inventions owned by the government remained the property of the agencies that developed them. It also established guidelines for the licensing of government-produced technologies to U.S. businesses.

■ **The Bayh-Dole Act** addressed technology developed by federal contractors and grantees. It authorized federal agencies to provide license agreements with private entities to develop federally owned inventions. The agencies could collect royalties for such licenses. Under the Act, businesses could profit from inventions or products developed from federally funded research.

The ultimate goal of these laws was the public benefit from federally conducted research. NIH’s goals in the technology transfer process emphasize public benefits over financial consideration.⁷¹ However, the financial success of certain drugs that benefited from government-funded research has raised concerns about whether the federal government is getting a fair return on its investment.

The GAO recently examined the public-private technology transfer process involving the cancer drug Taxol as a case study in federal technology transfer policies. The GAO determined that NIH’s total investment in Taxol-related research reached \$484 million and that five of the six studies submitted to FDA by Taxol manufacturer Bristol Myers Squibb (BMS)

Transferring technology from government-based laboratories to the private sector is an effort to bring new drugs to market more efficiently.

in support of its marketing approval were either conducted or funded by NIH. Furthermore, the federal government (via, for example, Medicare) has been a major purchaser of Taxol, paying over \$687 million from 1994 to 1999. The GAO found that NIH only received \$35 million in royalty payments from BMS.

In comparison, the GAO determined that BMS invested approximately \$1 billion in its efforts to bring Taxol to market and that worldwide sales for Taxol totaled over \$9 billion from 1993 to 2002. The GAO concluded that the NIH had invested heavily in research related to Taxol but that NIH's financial benefits—\$35 million through 2002—from the collaboration with BMS have not been significant in comparison to the drug's revenue.

A related concern is the inherent conflict of interest that can accompany public-private collaborations. Balancing the need to maintain the integrity of the distribution of public funds with the need to encourage successful public-private collaboration can be a challenge. The NIH's conflict-of-interest policies with respect to consulting practices of government officials in the private sector have come under scrutiny. The policies in place until now have allowed some NIH officials to earn large sums of money outside their government duties by consulting with private industries. In addition, the rules did not uniformly require full disclosure of the outside arrangements.

The NIH announced in August 2004 that a new oversight system will prohibit NIH employees with grantmaking powers from consulting for pharmaceutical or biotech companies. NIH indicates that other scientists will be allowed to consult because of the potential to speed the translation of research to cures; however, such consulting will be limited.

Purchasing

The passage of the MMA greatly expanded the government's role as a purchaser of prescription drugs. Providing a prescription drug benefit to 40 million Medicare beneficiaries, the MMA represents the most significant change to the entitlement program's benefit structure since its enactment in 1965. It will have a significant impact on the pharmaceutical market as well, particularly with respect to drug access, prices, and sales volume for the aged population—the industry's largest consumer group. Once the law is fully implemented, Medicare will become the largest purchaser of prescription drugs, although that purchasing power will be decentralized through private prescription drug and managed care plans.

Even before MMA, however, the government played a substantial role in purchasing prescription drugs. Federal and state governments have long been providers of prescription drugs to various programs and populations, but their role as purchaser is complicated. Industry representatives warn that too much consolidation of government purchasing power would amount to price setting, which would negatively affect R&D efforts and

The MMA will have a significant impact on the pharmaceutical market, particularly with respect to drug access, prices, and sales volume for the aged.

the rate of development of new products. Policymakers try to provide cost-effective access to prescription drugs for their populations in need without setting prices. As a result, a variety of drug purchasing programs, each different in design and administration, exist under the umbrella of government purchasing.

Medicaid, Medicare Part B, the Veterans Administration (VA), and the Public Health Service (PHS) each have different approaches toward purchasing prescription drugs. Though each secures prescription drugs at a discount, the size of the discounts and the methodologies for determining and securing the discounted prices differ. Further complicating the situation is that participation in certain programs is conditional on participation in others. This results in a complicated network of pricing and discount requirements for manufacturers wanting to sell their products to federal programs.

Medicaid — The Medicaid program is currently the largest single purchaser of prescription drugs, accounting for 17 percent of national prescription drug expenditures in 2002⁷²; in that same year, Medicaid spending reached \$250 billion and served over 50 million beneficiaries, including more than 6 million low-income Medicare beneficiaries (that is, dual eligibles).⁷³ Medicaid drug expenditures exceeded \$23 billion in 2002, with \$13.4 billion—approximately 58 percent of total drug expenditures—spent on dual eligibles.⁷⁴

The Medicaid Prescription Drug Rebate program was created in 1990 out of concern for the costs Medicaid was paying for outpatient prescription drugs. Though the rebates help state Medicaid programs receive discounts similar to what is provided in the nonfederal market, states are seeking new ways to contain their growing prescription drug costs. Medicaid drug spending has increased by more than 18 percent per year since 1997.⁷⁵

The Medicaid drug rebate program requires manufacturers to enter into agreements to provide states with rebates in order for their prescription drug products to be covered by Medicaid. The rebate formula is based on two industry-reported prices: the average manufacturer price (AMP) and the manufacturer's best price as paid by pharmacies in the retail trade and large private sector entities (that is, nonfederal purchasers). The rebate amount a manufacturer must pay for brand name drugs is the greater of 15.1 percent of the AMP or the difference between the AMP and the best price offered by the manufacturer to nonfederal purchasers. For generic drugs, manufacturers must provide 11 percent of the AMP rebate.

The accuracy of a manufacturer's reported pricing data directly affects the rebate amount owed. There is no uniform formula or definition of markets to be used for calculating AMP. As a result, different manufacturers include different markets in their AMP calculations, and the AMP can be undervalued, which lowers a manufacturer's rebate liability. AMP data is self-reported and considered proprietary, so the government generally does not audit manufacturers.

The Medicaid program, the largest single purchaser of prescription drugs, accounted for 17 percent of drug expenditures in 2002.

“Best price” determinations can be misrepresented as well. Certain discounts and fees (for example, partnership fees) paid by manufacturers to various purchasers as part of purchasing negotiations are not included in the definition of best price, yet they directly lower the price paid by some purchasers. By excluding these discounts and fees from the best price calculation, any drug’s best price can be inflated, which also results in lower rebate liability.

To help contain cost increases for Medicaid drugs, states have implemented a variety of policies aimed at limiting use of certain medications. These policies target expensive or risky medications and include the use of PDLs, prior authorization, increased cost sharing, limits on prescriptions, and “fail first” requirements (in which alternative, inexpensive drugs must be tried before an expensive one).⁷⁶ States are also implementing disease management programs to improve the effectiveness of treatment and care. The goal of these state cost-containment efforts is to reduce costs without reducing appropriate care.⁷⁷ However, such policies can have powerful effects on high-volume prescription drug users. Some of these cost-containment efforts may lose their appeal with the full implementation of the new Medicare outpatient prescription drug benefit when Medicare takes over the provision of such drugs to dually eligible beneficiaries.

Medicare Part B — Medicare Part B covers approximately 450 drugs and biologicals. Part B-covered drugs are purchased by physicians and other providers and are typically provided in an outpatient setting, such as a dialysis center or doctor’s office. Part B-covered drugs include non-self-administered drugs furnished “incident to” a physician’s services, self-administered oral cancer and anti-nausea drugs, immunosuppressive drugs, and certain vaccines. In 2002, Medicare spent more than \$8.4 billion⁷⁸ on outpatient drugs,⁷⁹ with most of that cost attributed to 35 drugs, primarily cancer, inhalation therapy, and oral immunosuppressive medications.⁸⁰

Payment for Part B drugs has undergone several changes and has been scrutinized for years. Medicare Part B drugs have been reimbursed based on the following models: the physician’s acquisition cost, 100 percent of AWP, the lower of the estimated acquisition costs or 95 percent of AWP, 95 percent of AWP, and 85 percent of AWP. The underlying problem with Part B reimbursement is that it has been found to exceed the actual prices at which providers are able to acquire the drugs, resulting in overpayment.

In an effort to address the overpayment issue, MMA established a new payment system based on manufacturer’s ASP. Manufacturers are required to report their drugs’ ASPs to the Centers for Medicare and Medicaid Services (CMS) on a quarterly basis. This is to ensure that reimbursement reflects market prices. The switch to payment based on ASP is expected to bring reimbursement in line with Medicare provider acquisition costs for drugs and biologics covered under Part B. Payment for Part B drugs

In 2002, Medicare spent more than \$8.4 billion on outpatient drugs, most of which is attributable to 35 medications.

has been highly controversial, however, and continuing debate surrounding these policies is likely.

VA — The VA purchases drugs based on actual prices paid by private purchasers. The VA negotiates directly with drug manufacturers to garner the discount prices available through the Federal Supply Schedule (FSS). The FSS is a catalogue of a broad range of products and prices available to federal government purchasers [for example, the VA and the Department of Defense (DoD)]. The FSS for pharmaceuticals contains over 23,000 products, including brand name and generic products, and is maintained by the VA. The VA purchases over 70 percent of the government's total prescription drug purchases from the FSS.

The amount of the discount depends on how successful the VA is in negotiating the price, but the goal is to obtain a discount equal to the largest discount given to most-favored nonfederal customers. Many FSS prices are as much as 50 percent below the nonfederal AMP.

There is a federal ceiling price that applies to roughly one-quarter of the schedule's drugs. However, these drugs represent approximately 75 percent of the dollars spent. The ceiling price, equal to 76 percent of the nonfederal AMP, can be accessed only by the VA, DoD, the Indian Health Service, and the Coast Guard.

The VA also uses competitive bidding to obtain favorable prices for certain drugs. Through competitive bidding, the VA can obtain national contracts for selected drugs that are priced lower than the FSS prices. In 2000, the VA contract prices averaged 33 percent less than corresponding FSS prices.⁸¹

Drug companies voluntarily participate in the FSS for several reasons. One is that participation in FSS is required in order to participate in Medicaid, which is a much larger percent of total U.S. sales. Another reason is that many physicians receive at least part of their medical training at VA hospitals, and the manufacturers have every incentive to have their drugs available to physicians in training who will theoretically continue to prescribe the same drugs when they leave the VA system. Finally, the percentage of U.S. sales subject to the discount is relatively small. Because the FSS was not designed for use by retail pharmacies, there is a clear delineation between retail pricing strategies and FSS pricing for manufacturers, such that providing FSS discounts will have a relatively small impact on other areas of business.

PHS Entities — Section 340 B of the Public Health Service Act establishes an up-front price break on prescription drugs for safety net providers who are not covered by the Medicaid drug rebate program or the federal ceiling price provisions under FSS. Organizations qualified to purchase at the discounts include Community Health Centers, Ryan White grantees, and ADAPs (AIDS Drug Assistance Programs). Manufacturers wanting to sell their products to these safety net providers must sign federal agreements to provide drugs at a discount, which is linked to

The VA can obtain national contracts for selected drugs; in 2000, contract prices averaged 33 percent less than corresponding FSS prices.

the rebate provided to the Medicaid program. Under the agreement, drug prices for 340 B entities cannot exceed a ceiling price that is defined in statute as AMP, less the Medicaid rebate percentage. Usually, the prices are in line with what Medicaid ultimately pays. Manufacturers wanting to participate in other federal programs such as Medicaid must sign 340 B federal agreements to provide drugs to these safety net providers at the 340 B prices.

Although manufacturers that want to sell drugs to the government under this program are required to sell them at a defined discount, 340 B entities are not required to purchase their drugs at that price. Some entities choose not to participate in the purchasing program because they believe they can negotiate better prices on their own. To simplify the process for obtaining 340 B drugs, the Health Resource and Services Agency (HRSA) has established a prime vendor program in which a single “preferred” wholesaler, AmerisourceBergen, supplies prescription drugs to covered entities at or below 340 B prices.

NEW CHALLENGES

The prescription drug market is changing. In addition to drug costs that continue to climb, new challenges on the horizon affect stakeholders individually and the market collectively. The government’s role in the market is changing as well, as policymakers continue to take steps to combat growing drug costs, provide cost-efficient access, encourage new drug development, and ensure safety.

The implementation of the new Medicare drug benefit will impact drug access, prices, and prescription volume for the industry’s largest consumer group, and it will also create new dynamics in the government’s role. The federal government will continue to rely on the retail market to determine prices; however, in an effort to minimize market disruption, there will be no set price ceilings or formulas as there are in other federal purchasing programs to contain costs.

A dynamic shift between state and federal governments will occur, and Medicare beneficiaries also eligible for Medicaid will now receive drug benefits through Medicare (instead of Medicaid). However, MMA’s “clawback” provisions require states to continue financing much of the cost of prescription drug coverage for the Medicaid population. States are concerned that they will remain financially at risk for drug costs but will not have direct control in how the prescription drug benefit is managed, giving them little ability to contain cost or influence quality of care.

It is also unclear whether the significantly increased federal role in financing prescription drugs will influence the other ways in which the federal government interacts with the prescription drug market. The ongoing debate related to the importation of prescription drugs suggests that regulatory and research policies may be shaped, in part, by financial

In addition to drug costs that continue to climb, new challenges are on the horizon that affect stakeholders individually and the market collectively.

concerns. Although policy discussions related to importation preceded the enactment of the Medicare drug benefit, many feel that the government's newly expanded financial stake in prescription drugs has helped to provide political traction for this issue. Similarly, many policy analysts are beginning to question whether FDA should consider cost-effectiveness in its approval process. Such a policy would be extremely controversial, and it remains to be seen whether Medicare financial pressures will have an impact on such debates.

These and other challenges will continue to generate much discussion in and out of Washington as the prescription drug marketplace, its various stakeholders, and the government evolve to meet their individual needs and maximize their positions within this very profitable and important sector of the U.S. economy.

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APPENDIX 1: Glossary

Accelerated Approval: A process used by FDA to speed approval of drugs promising significant benefit over existing therapy for serious or life-threatening illnesses.

Bioequivalence: Scientific basis on which generic and name brand drugs are compared. To be considered bioequivalent, the rate and extent to which the drugs are absorbed or otherwise available to the treatment site in the body cannot be significantly different.

Clinical Trials: Human studies designed to distinguish a drug's effect from other influences. Clinical trials conducted in the United States must be under an approved IND and in accord with FDA rules on human studies and informed consent of participants.

IND: Investigational New Drug application. Drug sponsors must submit an IND application to the FDA before beginning tests of a new drug on humans.

New Molecular Entity (NME): A compound that can be patented which has not been previously approved by FDA.

Parallel Track Mechanism: FDA policy that makes promising investigational drugs for AIDS and other HIV-related diseases available under special protocols while the controlled clinical trials for the drugs are being conducted. This mechanism is designed to make the drugs more widely available to patients who have no therapeutic alternatives and cannot participate in clinical trials.

Phase I Clinical Trials: The first trials in humans that test a compound for safety, tolerance and pharmacokinetics. The trials usually involve normal, healthy volunteers.

Phase II Clinical Trials: Pilot studies to define efficacy and safety in selected populations of patients with the disease or condition to be treated, diagnosed, or prevented.

Phase III Clinical Trials: Expanded clinical trials intended to gather additional evidence of effectiveness for specific indications and to better understand safety and drug-related adverse effects.

Phase IV: Studies performed after a drug is approved for marketing. Studies are used to determine incidence of adverse reactions and long-term effects of the drug and for marketing comparisons against other products and uses.

Preclinical studies: Studies that test a drug on animals and other nonhuman test systems.

Treatment IND: Mechanism for FDA to allow use of investigational products in expanded access protocols, which are generally unrestricted studies to learn more about a drug and provide treatment for people with immediately life-threatening or otherwise serious diseases for which there is no real alternative.

APPENDIX 2: Legislation Guide

Food and Drugs Act (1906): The first drug law. It required only that drugs meet standards of strength and purity. The burden of proof was on the government to show that a drug's labeling was false and fraudulent before it could be taken off the market.

Federal Food, Drug and Cosmetic Act (1938): Under this law, manufacturers were required for the first time to prove the safety of a drug before it could be marketed. This congressional action was prompted by the "elixir sulfanilamide" tragedy of 1937 in which over 100 people died from a poisonous ingredient in the product.

Kefauver-Harris Drug Amendments (1962): Considered the most significant change to U.S. drug law, the drug amendments of 1962 required drug manufacturers to demonstrate effectiveness for the product's intended use as well as its safety.

Stevenson-Wydler Technology Innovation Act (1980): Established that inventions owned by the government remain the property of the agencies that produce them. Also provided guidelines and priorities that encourage commercialization of government inventions through the licensing of technology to U.S. businesses.

Bayh-Dole Act (1980): Authorized federal agencies to execute license agreements with commercial entities to promote the development of federally owned inventions and to collect royalties for such licenses. Business, universities and nonprofit organizations can retain title to and profit from inventions arising from their federally funded research; however, the government retains the right to use the inventions without paying royalties.

Orphan Drug Act (1983): Allowed drug manufacturers to receive seven-year marketing exclusivity and tax deductions for the majority of the clinical trial costs for drugs and other products for treating rare diseases. Financial incentives are intended to encourage research and development of these "orphan" drugs which provide little or no profit to the manufacturer but may benefit people with these diseases.

Drug Price Competition and Patent Term Restoration Act (1984): This law allowed generic drug approval under abbreviated new drug applications, making it less costly and time-consuming for generic drugs to reach the market. The law also provided restoration of lost patent protection for innovator products.

Prescription Drug User Fee Act (1992): Established fees, including establishment fees, application fees, and products fees, to be paid by manufacturers. Fees were used to expand staff and quicken the new drug application review process.

FDA Modernization Act (1997): Contained sweeping changes to Food, Drug and Cosmetic Act of 1938, including the reauthorization of the Prescription

Appendix 2, continued

Drug User Fee Act. The act also codified FDA's accelerated approval regulations and required guidance on fast-track policies and procedures.

Medicare Prescription Drug, Improvement and Modernization Act (2003): Established a new voluntary outpatient prescription drug benefit under Medicare that will go into effect in 2006. Created a transition program involving drug discount purchasing cards effective in 2004. Replaced average wholesale price (AWP) as basis for prescription drug reimbursement under Part B with average sales price (ASP).