THE GREAT HEALTHCARE DEBATES
Prescriptions for meaningful reform.
To our clients and friends:

We are pleased to share the Medco 2009 Drug Trend Report, which chronicles an unprecedented year and identifies solutions for the historic challenges ahead.

As predicted, specialty drug trend accelerated dramatically, from 12.4% in 2007 to 15.8% in 2008. In addition, the price inflation of branded pharmaceuticals increased more than 8%. Despite these trends, Medco clients in 2008 realized an average drug trend of 3.5%—a small increase from our all-time low in 2007.

Among the insights revealed in this year’s report:

- The weak economy drove renewed interest in generics, as the generic dispensing rate increased 4.4% to 64.1%.
- About 30% to 40% of the medicines currently in the pipeline are specialty drugs, with nearly 25% of those targeting very rare conditions.
- Biologic or protein-based drug therapies account for about 16% of prescription drug spending and are growing at a much faster rate than other drug categories.
- Branded drug price inflation and unit-cost growth will be moderated by the wave of first-time generics in high-cost categories, which is expected to peak after 2011.

We would like to underscore a finding that reinforces mail as a successful quality and cost strategy: Clients with 40% or greater mail penetration had an average trend of -0.7%, while clients with less than 40% mail penetration had an average trend of 5.8%.

During the past year, Medco has proven that evidence-based, protocol-driven pharmacy practice can help lead a clinical transformation. Our specialist pharmacists across 14 Medco Therapeutic Resource Centers™ provide condition-specific patient care that is proven to close gaps in adherence and omission, and lower total healthcare costs. Linked to our pharmacogenomics collaborations with the Mayo Clinic and other leading institutions, we are forming a foundation for greater mail penetration.

Sincerely,

David B. Snow, Jr.
Chairman and CEO

Robert S. Epstein, M.D., M.S.
Senior Vice President, Chief Medical Officer

PS: For additional copies of this report, please contact your Medco account representative. A searchable PDF is available at www.drugtrend.com

To download a searchable PDF of the full 2009 Drug Trend Report, go to www.drugtrend.com.

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# 2009 DRUG TREND REPORT

## TABLE OF CONTENTS

### EXECUTIVE SUMMARY 2–17

### SPOTLIGHT ON TREND FOR 2008 | UNIT COST VS. UTILIZATION 18–45
- 2008 drug trend overview ........................................... 19
- Unit cost ............................................................... 20
- Utilization ............................................................. 25
- Drug trend drivers and moderators .............................. 30
- Specialty healthcare .................................................. 37
- Medicare trend ......................................................... 39
- Demographics of trend .............................................. 41
- National trend ........................................................ 44

### THE DYNAMICS OF FUTURE TREND | GENERICS VS. SPECIALTY DRUGS 46–81
- Trend projections ..................................................... 47
- Market projections ................................................... 50
- Cardiovascular agents .............................................. 57
- Central nervous system agents .................................. 62
- Endocrine and diabetes agents .................................. 67
- Musculoskeletal and rheumatological agents ............... 70
- Respiratory agents .................................................. 75
- Oncology agents ..................................................... 78
- Other therapeutic agents ......................................... 81

### SETTING THE STAGE FOR REFORM | PHARMACY AT THE FOREFRONT 82–99
- Challenges in the current system ............................... 83
- Wiring the healthcare system .................................... 86
- Improving healthcare: Leveraging the pharmacy model .. 90
- The future of healthcare .......................................... 99

### REFERENCES 100–108
EXECUTIVE SUMMARY
Factors contributing to 2008 drug trend

2008 drug trend for Medco clients was 3.3%.* The primary driver of trend shifted from utilization to unit cost—unit costs increased 4.4% and utilization growth declined 1.1%. Drug trend excluding specialty drugs was 1.3% in 2008.

**UNIT COST**

The unit-cost increase of 4.4% observed in 2008 was substantially higher than the 0.4% increase seen in 2007. The primary contributing factors to unit-cost increases in 2008 included:

- Significant price inflation of branded pharmaceuticals
- Growth of specialty drug spending due to the introduction of new high-cost brands in 2007 and 2008
- Higher use of existing specialty drugs

**GENERIC DISPENSING RATE**

Generic drugs account for the majority of prescriptions filled by plan members served by Medco. This helped to moderate the increase in unit costs. In 2008, the average generic dispensing rate (GDR) for Medco clients was 64.1% compared with 59.7% in 2007 (Figure 1).

Figure 1. Frequency distribution of generic dispensing rates

Source: Medco data

Note: The figure shows the generic dispensing rates achieved by Medco clients during the fourth quarter of 2008. The generic dispensing rate is the percentage of prescriptions dispensed as generic drugs. Data are shown for clients with integrated benefits (plans that include both retail and mail-order options for their members).

**PRICE INFLATION**

In 2008, the price inflation of branded pharmaceuticals used by plan members was a major contributor to the increase in unit costs. Over the last 5 years, the price inflation of branded drugs has continued to increase while the price inflation of generic drugs has hovered at approximately 0.5% (Figure 2). During the past 5 years, increases in the price inflation of branded drugs greatly outpaced the overall price inflation of goods and services, as measured by the consumer price index, for the same time period.†

* Reported trends are based on 2 years’ data on pharmaceutical spending and carriers with significant enrollment changes (e.g., an increase or decrease of greater than or equal to 50%) were not included in the analysis. This sample represents 77% of the $38.9 billion spent by Medco clients with integrated benefits (plans that include both retail and mail-order options for their members). Plan spending is reported on a per-eligible per-month basis, unless otherwise specified. Plan spending is the net cost to plan sponsors after discounts, rebates, subsidies, and member cost share have been applied. Drug trend is the percent change in plan spending from one year to the next.

† The consumer price index (CPI) measures the change in the cost of a fixed market basket of goods and services. The CPI is calculated by the Bureau of Labor Statistics (BLS) and is used as one of the main indicators of inflation in the U.S. It is expressed as a percentage change from a base year (usually 2007). The CPI is a weighted average of prices of a basket of goods and services such as food, energy, clothing, and shelter. The weights used in the CPI are based on the spending patterns of a typical urban consumer.
INTRODUCTION OF NEWER HIGH-COST DRUGS

The number of new high-cost drugs that were approved in 2007 and 2008 also drove unit-cost growth during 2008, with about one-third of the new drug introductions for high-cost drugs that treat cancer, pulmonary arterial hypertension, and various immune-related or orphan conditions. In addition, many of these new high-cost drugs were within the specialty category.

UTILIZATION

For the first time in the last decade, overall drug utilization declined (1.1%). The factors likely to have contributed to this decline included:

- Prescription to over-the-counter conversions of Zyrtec® and Miralax®
- Safety concerns within several classes of drugs (osteoporosis therapies, hormone replacement therapy, erythroid stimulants)
- The launch of a limited number of new drugs, many of which were primarily indicated for low-prevalence conditions

The changing economic climate in 2008 has refocused benefit plans and their plan members on lower-cost alternatives. For example, more members are utilizing more generics; the GDR for Medco’s clients increased 5% for mail prescriptions and 4.3% for retail. Also, more members are choosing to fill their prescriptions by mail—mail-order volume increased substantially from 2007. Both of these metrics suggest that members are taking advantage of the cost savings associated with use of generics and mail order.

TREND DRIVERS AND MODERATORS

Three broad therapeutic categories—central nervous system (CNS), cardiovascular, and gastroenterology—contributed to approximately half of all drug spending in 2008. Other significant contributors were medications from the endocrine/diabetes, respiratory, anti-infective, and musculoskeletal/rheumatology therapeutic categories. The 10 therapeutic classes that had the largest impact on trend in 2008 are shown in Figure 3. Spending increased for all of these therapeutic classes, but spending declines for lipid-lowering drugs and allergy medications helped to moderate the overall trend.

SPECIALTY HEALTHCARE

Despite relatively small prescription volumes, specialty drugs were a major driver of spending growth and a significant component of pharmacy spending. In 2008, specialty drug spending grew 15.8%, up from 12.4% in 2007. Specialty drugs accounted for 12.8% of total pharmacy spending in 2008, up from 11.4% in 2007.
Unit costs for specialty drugs increased 11.5%. The primary contributors to this increase included:
- Price inflation of specialty drugs
- The significant proportion of new drug approvals for high-cost specialty drugs
- Dosage creep or dosage increase among some specialty drugs

Utilization of specialty drugs increased 4.3% in 2008. Utilization growth was driven by several factors including:
- Increasing use of tumor necrosis factors (e.g., Enbrel® and Humira®)
- Increasing number of treatment options and treatment combinations for pulmonary hypertension
- Reallocation of some specialty drugs from coverage under the medical to pharmacy benefit
- Increased use of specialty drugs for new indications

Note: This figure shows the contribution of the top 10 therapeutic classes to overall trend in 2008. Therapeutic classes are rank-ordered from the largest positive contributor (at the top) to the smallest positive contributor (at the bottom). The figure also shows the year-over-year changes for plan cost (drug trend), utilization (days per eligible), and unit cost (cost per day) for these 10 classes. Spending growth factors multiply to yield total trend, so utilization growth and unit-cost growth may not be additive.

* Includes treatments for Alzheimer’s and Parkinson’s diseases.
The growth in pharmacy spending for specialty drugs was concentrated in a small number of therapeutic areas (Figure 4).

- Spending increases were highest for drugs used to treat rheumatoid arthritis and other autoimmune disorders, psoriasis, multiple sclerosis, and cancer.
- For pulmonary arterial hypertension and anticoagulation, utilization growth was the primary contributor to trend.
- For cancer and multiple sclerosis, increased unit costs were the primary driver of trend.
- Spending declines were seen for drugs that treat anemia and hepatitis C.

**MEDICARE TREND**

As of February 2009, there were 45.2 million elderly and disabled retirees eligible for Medicare Part D and 26.7 million beneficiaries enrolled. The number of eligible recipients is expected to increase dramatically over the next two decades and Medicare will continue to be a significant driver of trend. Medicare and Medicare Advantage prescription drug plan costs increased by 6.8%. Unit costs for Medicare enrollees increased 4.7% and utilization grew 2.1%. Costs for employer-primary coverage plans increased 6.5% with unit costs and utilization increases of 3.2% and 3.3%, respectively.

The top 5 categories of prescription drug spending for Medicare enrollees in 2008 were cardiovascular (29.5%), central nervous system (19.5%), gastroenterology (10.1%), endocrine/diabetes (8.4%), and respiratory (7.5%). Two of the classes within the cardiovascular category—lipid-lowering and antihypertensive drugs—accounted for almost 25% of the spending (Figure 5). The most rapid plan-cost increases were seen in selected neurological, cancer, transplant, and respiratory drugs, with sharp declines seen for allergy and lipid-lowering drugs. The majority of Medicare trend was driven by increases in unit costs, with use of single-source brand-name drugs driving this acceleration.

Selected neurological, seizure, and antipsychotic drugs were the primary drivers of Medicare utilization. Although utilization growth accelerated for lipid-lowering drugs (3.5%), it was offset by a significant reduction in unit costs (-7.5%) due to the increased use of generics.

**NATIONAL TREND**

National drug trend for 2008 is estimated at 3.5%, which is significantly slower than the growth rates for both hospital care (7.2%) and physician and clinical services (6.2%). The Centers for Medicare & Medicaid Services (CMS) posits that the slowdown for prescription spending is likely due to the effects of the recession, which may be causing consumers to shift from more expensive brand-name drugs to lower-cost generics and to fill fewer prescriptions.

CMS projects an acceleration of national drug spending in 2010, likely based on:

- Anticipated improvements in economic conditions
- New indications of currently approved drugs
- Faster pace of growth among generics

* The analysis of Medicare trend is based on 2 years’ data on pharmaceutical spending by enrollees in Medicare Part D (PDP, MA-PD) plans managed by Medco. Plan spending is the net cost to plan sponsors after discounts, rebates, subsidies, and member cost share have been applied. The analysis does not include prescription drug spending under Medicare Part B.

† The analysis of Medicare trend is based on 2 years’ data on pharmaceutical spending by enrollees in commercial (employer-primary) plans managed by Medco. Plan spending is the net cost to plan sponsors after discounts, rebates, subsidies, and member cost share have been applied. The analysis does not include prescription drug spending under Medicare Part B.

‡ Selected neurological includes treatments for Alzheimer’s and Parkinson’s diseases.

The respiratory category includes treatments for asthma, COPD, and pulmonary arterial hypertension but does not include treatments for allergies or colds.
Trend forecast: The next 3 years

Over the next few years, drug trend will be shaped by several forces including:
- Increase in new and existing specialty and protein-based drugs for common and rare conditions
- High price inflation among branded traditional and biotech brands that lack generic competition
- Unit-cost growth, which will be moderated by the wave of first-time generics for traditional drugs in high cost categories expected to peak soon after 2011
- Modest increases in treatment rates
- Greater use of therapeutic approaches relying on genomic information and genomic testing in order to personalize therapy

Based on existing plan designs and coverage provisions, Medco expects the average ingredient cost-based drug trend for plan sponsors to increase between 3% and 7% annually over the next 3 years, with the lower single-digit trends towards the beginning of this period (Table 1).

Table 1. Drug trend projection for 2009–2011*

<table>
<thead>
<tr>
<th>Year</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
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<tbody>
<tr>
<td></td>
<td>Utilization increase</td>
<td>0% to 1%</td>
<td>0% to 1%</td>
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<tr>
<td></td>
<td>Price and mix increase</td>
<td>3% to 4%</td>
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</tr>
<tr>
<td></td>
<td>Annual total</td>
<td>3% to 5%</td>
<td>4% to 6%</td>
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*Projected change in drug spending on a plan ingredient cost per-member per-year (PMPY) basis

** KEY TREND DRIVERS**

Over the next 3 years, more than 85% of drug trend will be driven by drugs in six categories: cardiovascular, endocrine/diabetes, central nervous system, musculoskeletal/rheumatology, respiratory, and oncology.
- Cardiovascular and endocrine/diabetes categories will account for about 40% of the spending growth.
- Diabetes treatments, anticoagulants/antiplatelet therapies, antihypertensives, rheumatological drugs, lipid-lowering drugs, and oncology drugs will account for almost 60% of ingredient cost spending growth over the next 3 years.

Future unit costs and utilization will likely be impacted by several factors such as:
- New specialty and traditional drug approvals
- New or expanded indications for existing drugs
- Use of new pharmacogenomic testing approaches
- New dosage forms
- New combination products
- Patent expirations and first-time generics
- Expected OTC conversions
- Research findings and clinical recommendations likely to affect prescribing practices
- Changes in disease prevalence, disease recognition, or diagnostic/treatment criteria
Market projections

- **NATIONAL DRUG TRENDS**

CMS predicts that the average annual increase in national drug expenditures over the next 10 years will be between 6% and 7%. Specifically, the growth will be 3.5% in 2008, 4.5% in 2010, and 6.6% in 2013 and is then expected to accelerate to 8.6% by 2018.3

The volume of first-time generic introductions in 2011 and 2012 will moderate the growth in 2012 and 2013. However, first-time generics will decrease in 2014 and, coupled with new drug introductions after 2014, will result in accelerated growth from 2014 to 2018.

- **DRUG PIPELINE**

Approximately 30% to 40% of drugs in the pipeline (2009-2011) are likely to be specialty drugs. Almost a quarter of these will be used to treat “orphan” conditions.

Drugs for the treatment of cancer continue to be the largest area of new drug development (Figure 6).4 Some of these new drugs, especially in the oncology area, will be more targeted therapies that will use genetically based or biomarker information from patients or tumor biomarkers to determine who should and should not receive these drugs.

During the next few years, a number of new specialty and nonspecialty blockbuster drugs for cancer, diabetes, immunological diseases, cardiovascular disorders, and pain are anticipated. Some possible future blockbusters include prasugrel (an antiplatelet drug for preventing thrombotic events), rivaroxaban (a new oral anticoagulant), denosumab (an injectable biologic for osteoporosis), ustekinumab (a biologic for psoriasis), golimumab (a tumor necrosis factor inhibitor for rheumatoid arthritis), and naproxcinod (a novel nonsteroidal anti-inflammatory drug [NSAID] that releases the chemical nitric oxide).

- **FIRST-TIME GENERICS**

Drugs with total 2008 U.S. sales of nearly $34 billion could lose patent protection over the next 3 years, expanding the potential market for lower-cost generics. Between now and 2012, first-time generics will represent slightly more than half of the total of about $66 billion in current drug spending that could be affected by generic competition over the next 5 years. These first-time generics represent a significant opportunity for savings and a means to help offset some of the new costs associated with drug introductions over the next 5 years.

- **PERSONALIZED MEDICINE**

Integration of this genomic technology into day-to-day healthcare will take years to fully achieve, but events during the next few years are likely to shape the evolution of personalized medicine. The greatest impact in drug selection over the next few years is likely to come from identification of biomarkers relating to existing and...
near-term pipeline drugs, particularly those with questionable efficacy, high toxicity, or considerable dosing variability. Several drugs in the pipeline are being co-developed with molecular diagnostic tests (also called “companion diagnostics”) that help identify the target treatment population.

- **BIOSIMILARS**

  Protein-based drug therapies account for about 16% of spending on prescription drugs, and the drug trend for biologics is growing at a much faster rate than for their pharmacologic counterparts. The lack of availability of lower-cost competitors is one of the factors contributing to the rapid growth in spending for these drugs. Already approved in the European Union, several proposals have been made to create a pathway to market for follow-on biologics (biosimilars) in the United States. The first biosimilar product could come to market within a year or two after the pathway is approved.

- **PRESCRIPTION TO OVER-THE-COUNTER (OTC) SWITCHES**

  The conversion of prescription drugs to OTC status is a trend that will continue. OTC versions of Zyrtec (cetirizine), a nonsedating antihistamine, came to market in 2008. OTC conversion of another nonsedating antihistamine, Clarinex® (desloratadine), is expected in 2009. Novartis has acquired the rights to market OTC versions of Prevacid® (lansoprazole) and is expected to launch an OTC version when the patent on the brand expires in late 2009. As with Prilosec OTC®, the OTC conversion for Prevacid may be only partial, with different strengths or formulations available in prescription and OTC form.

- **KEY THERAPEUTIC DEVELOPMENTS**

  Diabetes, anticoagulant and antiplatelet, respiratory disease, and rheumatological drugs represent the main trend-driving categories for the next 3 years. Specialty, biologic, and orphan drugs for the treatment of cancer, as well as non–cancer-related indications, will become increasingly important trend drivers. As more patents expire on blockbuster small-molecule drugs, future blockbusters will come from products within the biologics category. Following are trend projections for three of the largest therapeutic categories:

**Cardiovascular agents**

Contribution to plan spending (2008): 22%
Projected contribution to trend (2009 to 2011): 22%

- **PROJECTED TREND**

  Table 2. Drug trend projection for cardiovascular agents*

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<td>2% to 3%</td>
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<tr>
<td>Price and mix increase</td>
<td>2% to 3%</td>
<td>5% to 6%</td>
<td>5% to 6%</td>
</tr>
<tr>
<td>Annual total</td>
<td>2% to 4%</td>
<td>7% to 9%</td>
<td>7% to 9%</td>
</tr>
</tbody>
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*Projected change in drug spending on a plan ingredient cost PMPY basis
Central nervous system (CNS) agents

Contribution to plan spending (2008): 22%
Projected contribution to trend (2009 to 2011): 14%

TREND PREDICTIONS
Key developments that are likely to shape drug trend in the CNS category over the next 3 years:
- Continued growth in utilization of the antiseizure and antipsychotic medications
- New drugs for the treatment of MS, epilepsy, schizophrenia, depression, and migraine
- New pain medications and reformulations of narcotic pain relievers to discourage abuse
- Increased use of new and existing drugs for fibromyalgia, a pain syndrome
- First-time generics for Imitrex® (sumatriptan), a commonly used antimigraine agent; Topamax® (topiramate), a commonly used antiseizure agent; Adderall XR® (amphetamine salts), a stimulant commonly used for attention deficit hyperactivity disorder (ADHD); Effexor XR® (venlafaxine extended release), an antidepressant; and Aricept® (donepezil), an agent for dementia

Trend drivers: Narcotic pain relievers, atypical antipsychotics, branded antidepressants, MS agents
Trend moderators: NSAIDs, selective serotonin reuptake inhibitors, antiseizure medications, sleep agents
Endocrine and diabetes agents

Contribution to plan spending (2008): 8%
Projected contribution to trend (2009 to 2011): 18%

PROJECTED TREND

Table 4. Drug trend projection for endocrine and diabetes agents*

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<tr>
<th>Year</th>
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<th>2010</th>
<th>2011</th>
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<tbody>
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<td>Utilization increase</td>
<td>1% to 2%</td>
<td>1% to 2%</td>
<td>1% to 2%</td>
</tr>
<tr>
<td>Price and mix increase</td>
<td>9% to 10%</td>
<td>7% to 8%</td>
<td>9% to 10%</td>
</tr>
<tr>
<td>Annual total</td>
<td>10% to 12%</td>
<td>8% to 10%</td>
<td>10% to 12%</td>
</tr>
</tbody>
</table>

*Projected change in drug spending on a plan ingredient cost PMPY basis

TREND PREDICTIONS

Key developments that are likely to shape drug trend in the endocrine and diabetes category over the next 3 years:
- Continued rapid growth in utilization of diabetes drugs because of the epidemic of obesity and diabetes in this country
- Increased use of multiple-drug therapy to help control blood glucose levels and prevent long-term complications of diabetes
- Introduction of several new oral and injectable agents for the treatment of diabetes and its complications
- Very limited first-time generic introductions

Trend drivers: New users of oral hypoglycemic agents, insulin products
Trend moderators: None
America’s healthcare system today is fragmented, inefficient, and often ineffective; quality of care and cost of care are out of sync, and costs are unsustainably high. National healthcare reform has become an urgent priority for public policy leaders.

An estimated 47 million people have no healthcare coverage or are underinsured and, in the current economic climate, this will likely increase. Those involved in the delivery of healthcare have an opportunity to provide responsible leadership and solutions that will improve clinical and financial outcomes.

Challenges in the current system

- **A CHASM BETWEEN COSTS AND CLINICAL OUTCOMES**

  Healthcare spending increases are now unsustainable. National healthcare spending is expected to double, from $2.4 trillion in 2008 to $4.4 trillion by 2018. The value provided, however, is not commensurate. The United States has lower life-expectancy rates than many other developed countries, despite per capita spending that is twice as high.

- **HEALTHCARE “UNWIRED”**

  Unlike the pharmacy care system, American healthcare is not wired. In the clinical setting, the majority of healthcare providers act independently, without the benefit of complete, real-time knowledge of a patient’s past and current medical history or insurance coverage. This impacts the quality of care as well as overall costs, making coordinated care virtually impossible and increasing the prevalence of dangerous medical errors. A review involving the medical records of 41 million Medicare patients identified $8.8 billion in error-associated costs and 238,837 preventable deaths. Moreover, a large subset of these errors are medication errors. An estimated 1.5 million preventable serious medication errors occur each year, with $217 billion (2006 dollars) in associated costs.

- **INEFFECTIVE MANAGEMENT OF COMPLEX AND CHRONIC DISEASE**

  The cost of care for patients with chronic disease is overwhelming. Half of all Americans are being treated for at least one chronic condition and drugs are the first intervention in nearly 90% of these cases. These patients account for 75% of all medical costs and 96% of all drug spending. An estimated $1 trillion annual reduction in both direct and indirect costs associated with chronic and complex diseases could be achieved with better prevention, detection, and treatment.

Wiring healthcare

> “The U.S. healthcare marketplace’s continuing failure to adopt information technology (IT) is the result of economic problems unique to healthcare, business strategy problems typical of fragmented industries, and technology standardization problems....”

> —J.D. Kleinke, Executive Director, Omnidex Institute, a nonprofit healthcare research and information technology development organization based in Portland, Oregon

Care that is delivered in a wired environment enables:

- Evidence-based protocol-driven decision making
- Access to complete diagnostic, laboratory, health, and treatment records
- Real-time data collection for measuring every aspect of care that can be used to evaluate and improve current practices and patient outcomes
- A standardized rewards system based on the contributions that add value to the system

One study estimated that over a 15-year period, the savings from using electronic medical records in the hospital setting could exceed $370 billion; in the ambulatory setting, the forecasted benefit was similarly impressive at $142 billion.
The need to wire healthcare has been clearly acknowledged by the new administration. The American Recovery and Reinvestment Act of 2009, signed into law by President Obama, includes $2 billion in funds for grants and loans from the Office of the National Coordinator for Health Information Technology to facilitate the adoption of HIT. Another $17.2 billion is set aside for Medicare and Medicaid to reward hospitals and physicians with financial incentives for using electronic systems.12

**PROTOCOL-DRIVEN HEALTHCARE**

The systematic adoption of protocol-driven, evidence-based healthcare, which is possible only with a fully wired framework, is necessary to improve effectiveness and efficiency, enhancing outcomes and reducing costs.

A healthcare protocol is a recommended course of action based on an assessment of the best evidence. Many healthcare providers are reluctant to embrace protocol-driven care largely over the perceived interference with professional medical judgment. In fact, healthcare protocols are not designed to substitute for the experience of a physician, but rather complement that experience. In today’s environment, the rate of scientific discovery challenges an individual physician’s ability to keep pace. Wiring the system and adhering to protocols have proven to be effective tools to ensure consistency in care and improve patient outcomes.

Safety in clinical practice is contingent on a structure that reduces errors and increases the likelihood of favorable outcomes. By reducing variation and increasing compliance associated with accepted standards of care, protocols represent a “quality” approach to continuous improvement.

**THE BENEFITS OF WIRED PROTOCOLS—PHARMACY AND DUR**

Drug utilization review (DUR), the process of screening prescriptions for potential drug-related problems, has been a part of pharmacy practice for more than 25 years. DUR is now considered part of the baseline standard of care for the practice of pharmacy and provides an excellent example of how protocol-driven practice complements professional judgment.

Not all DUR is the same, however. For example, Medco uses an advanced DUR system with additional safety provisions that are optimized for seniors, who as a population take the most medicines and face unique challenges. The value of this enhanced system was borne out by a Medco study to determine if the DUR alerts combined with pharmacist-initiated provider contact improved clinical care.13 Approximately 43,000 safety alerts were triggered during the 12-month study period. In 56% of those cases, pharmacists specializing in geriatric care contacted prescribing physicians. The communication resulted in a 24% rate of change; much higher than the expected 2% DUR change rate that had been reported in the literature. This landmark study demonstrated that DUR, as part of a wired environment, enables a level of pharmacy care management that improves quality and enhances safety.

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**Improving healthcare: Leveraging the pharmacy model**

“In an era when preschoolers use the Internet to chat with friends half a world away, it is inexcusable that doctors write paper prescriptions—in Latin—which patients need to take to another professional in a process fraught with countless opportunities for error.”

—David B. Snow, Jr., Chairman and Chief Executive Officer, Medco Health Solutions, Inc.

Addressing identified clinical gaps is an essential component of improving care. Clinical gaps in care include nonadherence, errors of omission, and errors of commission. The pharmacy model provides a blueprint for closing these gaps by using technology—wiring the pharmacy system and using protocols to administer care.
MEDICATION ADHERENCE

“Effective ways to help people follow medical treatments could have larger effects on health than any treatment itself.”
—Cochrane Database Review

It is well known that a link exists between adherence (taking drugs as prescribed) and successful clinical outcomes. In one study, patients who took their cholesterol-lowering drugs as prescribed by their physicians had significantly greater survival rates compared to their nonadherent counterparts (Figure 7).14

Even when the proper medicines are prescribed, however, it is estimated that as many as 50% of patients abandon their prescribed therapy in the first year of treatment.15 Pharmacists, considered among the most trusted professional in America, play a critical role in improving medication adherence. One study involving patients under care for heart health and other chronic disease16 used patient counseling and educational techniques that, within 6 months improved adherence to prescribed medications by at least 90% (from 5% to 98.7%), and, not surprisingly, blood pressure and cholesterol levels, two indicators of overall health, were lower.

ERRORS OF OMISSION AND COMMISSION

For most common medical conditions, practitioner preference guides initial therapy choices. When a protocol-based disease management guideline outlines therapeutic choices, an error of omission occurs if a patient is not prescribed one or all of the necessary medications based on the diagnosis or the condition.

In pharmacy care, mistakes can be life-threatening. The prevalence of errors dictates that we implement strategies to reduce the risk in every step of the process. There are multiple opportunities for errors to occur during the prescription process. Errors occur during the prescribing stage (e.g., wrong drug, wrong dose, allergy), dispensing (e.g., wrong drug, wrong dose, interactions, allergic reactions), administration (e.g., wrong time, wrong patient), and monitoring. Understanding the process and identifying where mistakes can occur is the first step towards addressing and correcting these errors.
In order to ensure success, technology must be coupled with protocol-driven care and continuous improvement programs to yield measurable progress in closing the gaps in care. Fully wired systems will facilitate the evaluation of clinical decisions as well as more quickly identify possible new sources of error that must be addressed. This continuous feedback loop provides the real-time data necessary to improve care and outcomes.

**BUILDING ON INNOVATION IN PHARMACY PRACTICE**

Pharmacy provides a proven example of the benefits cascading from a wired healthcare delivery system by using leading-edge technology to support protocol-driven healthcare, facilitate communication, and improve patient outcomes.

Prescription data transactions are real-time, capturing clinical and financial information for each claim. Additionally, wired systems that support e-prescribing can efficiently transfer prescription information, improve formulary compliance, and reduce errors associated with interpretation of prescriber handwriting by the pharmacist. Recognizing the importance of e-prescribing is underscored by the emergence of government-based incentive programs, whereby physicians are financially rewarded for adopting e-prescribing and will be penalized beginning in 2012 if they fail to do so. Private-sector health insurance plans are also moving in this direction.

E-prescribing systems provide decision-support tools to prescribers that are designed to improve evidence-based drug selection and streamline processes; notify physicians of potential drug interaction, drug allergies, formulary status issues, generic availability, and dosing; and advise on whether or not a prescription has been filled.

The success in speeding innovation in the practice of pharmacy provides a roadmap for a broader application of technology across the healthcare continuum. What began with building a wired system that allowed users access to essential information became the platform to build new applications that addressed accuracy, efficiency, contraindications, and pharmacological history to facilitate informed decisions. Applying this success would be a natural progression for far-reaching healthcare reform.

**REINVENTING PHARMACY CARE**

The Medco Therapeutic Resource Centers® model is clinically innovative and results-oriented. Recognizing the overwhelming impact of chronic and complex diseases on healthcare spending, Medco completely reinvented its pharmacy practice model. Chronic and complex conditions are part of everyday life for 50% of Medco’s members. These members account for approximately 96% of pharmacy costs and 75% of medical costs. Medco’s model focuses the most efficient use of resources, helping to deliver the highest clinical quality at the lowest cost.

Each of Medco’s therapy centers focuses on the care of patients with specific conditions, such as asthma, heart disease, or diabetes, paralleling the physician-specialty model. The therapy centers are staffed by pharmacists who receive specialized training in these conditions and immerse themselves in daily practice tending to the medication-related needs of these patients.

The concept of the Medco Therapeutic Resource Centers pairs specialized pharmacist knowledge with available patient data by leveraging technology to apply evidence-based protocols to improve patient care. In effect, this care model represents a microcosm of key components of healthcare reform—wiring, protocols, and process improvement through feedback loops. The results demonstrate better adherence, improved care, fewer errors, and reductions in cost.

The therapy center structure enables pharmacists to consult with physicians so that the patient receives the appropriate therapy at the optimum dose and that the relevant protocol is followed. Specialized pharmacists can have more informed and impactful discussions with patients and physicians due to their knowledge of a specific chronic or complex disease. This approach aligns the patient, physician, and pharmacist with the patient’s treatment goals, and helps ensure that patients remain adherent with the physician’s prescribed treatment regimen.
IDENTIFYING AND CLOSING GAPS IN CARE

Using analytic capabilities, Medco developed a proprietary Health Action Plan to precisely identify patients who have gaps in care associated with the treatment of their chronic condition. In discussions with the patient, the specialist pharmacist reviews this evidence-based algorithm, which creates an opportunity for a “teachable moment”—when the patient is receptive to counseling. By striving to close the gaps in care (e.g., the patient is not receiving a medication or is not being monitored according to standards of care) pharmacists assess and address barriers to compliance, which allows them to correct errors, modify behaviors, leverage cost-savings opportunities, and connect patients with other available resources.

The protocol-driven care model of the Medco Therapeutic Resource Centers is an example of a fully wired system. 100% of prescription drug data and available complementary medical information are used to identify and close gaps in care, proactively improve care, and prevent medication errors. This real-time approach to the care of chronically ill patients is a significant step forward in improving clinical outcomes and reducing healthcare spending, which is unprecedented in large-scale pharmacy operations.

ADVANCING PHARMACOGENOMICS TO IMPROVE DRUG THERAPY

“The selection of a drug based on genomic biomarker profile is desirable because it limits drug exposure to patients who will benefit/are most likely to benefit from drug treatment, avoids drug use in patients who will be/are likely to be harmed by drug treatment, or enhances safe use by optimizing drug dosing.”
—FDA briefing document for the December 16, 2008, meeting of its Oncologic Drugs Advisory Committee

Pharmacogenomics—understanding the relationship between drug response and genetics—is the future of pharmacy. Information on how a patient will respond to medicines based on his or her unique genetic disposition is now available in product labels for about 25% of patients taking drugs approved by the FDA.¹⁷

Genetic information is proving to be a reliable guide to the physician in determining which medications will—or won’t—work and which dose is optimal based on that particular patient’s unique genetic profile. This information is typically made available through a relatively low-cost test that is often as easy as providing a sample with a cheek swab.

According to a survey of large employers, the number of plans that will provide coverage for genetic testing is expected to increase from 15% to about 40% over the next 3 to 5 years as more doctors realize the value of testing and more tests are available for a growing number of medications.

In the future, DUR rules will also incorporate genetic information. If the entire healthcare system were wired, this information would be readily accessible by caregivers to make informed therapy decisions, optimizing outcomes and minimizing adverse effects.
The future of healthcare

Our country faces monumental healthcare challenges. Despite unprecedented financial strains, the United States will continue to address the needs of large numbers of people who are afflicted with multiple chronic diseases—whose treatment includes multiple physicians prescribing multiple regimens of medications.

When patients cannot afford or do not take their medicines, or their treatment is not consistent with evidence-based protocols, tragic complications and consequences are inevitable, the costs are unsustainable, and the goal of extending care to the uninsured becomes impossible.

Medco’s pharmacy paradigm has demonstrated:
- Pharmacists with specialized training and guided by real-time data matched against evidence-based protocols can efficiently identify and close clinical gaps in care.
- Closing gaps in care improves patient outcomes and reduces costs.
- A wired, advanced pharmacy environment enables measurement; makes prescribers, patients and pharmacies accountable; and delivers transparency to payers.

Medco is committed to sharing what it has learned. The company will publish its research findings in peer-reviewed journals and share the results at professional conferences. Additionally, Medco has already begun evaluating ways to work with community pharmacies to bring the benefits and solutions that have been created in the Medco Therapeutic Resource Centers to the patients they serve. Medco is also working with policymakers in Washington, D.C., with the hope that the therapeutic center model contributes to the healthcare reform efforts under consideration today.

PRESCRIPTIONS FOR REFORM

Here are three action steps we can all take to foster meaningful healthcare reform:
- **Promote a common health information technology (HIT) platform.** Support the development of a common platform to share essential data with all who are involved in healthcare delivery. Key to the success of the wiring effort will be government involvement to set rules to promote open software platforms that can easily accommodate new and improved applications so that competition and flexibility will encourage innovation and ultimately lower costs. E-prescribing is a key component of a wired system that has proven benefits for pharmacy and healthcare.
- **Encourage widespread adoption of protocol-driven care.** In a wired system, protocols can be seamlessly incorporated to improve the effectiveness, efficiency, and safety of care delivery. Results can be monitored to assess clinical outcomes, and protocols can be modified based on new data or study results.
- **Incent providers to adopt HIT systems and protocol-driven care.** This will facilitate e-prescribing and systematic use of evidence-based protocols. Improved outcomes and reduced costs will then follow in time.

Working together, stakeholders are:
- Harnessing the power of technology
- Connecting communities of practice
- Driving the use of evidence-based protocols
- Leveraging measurement to foster accountability
- Rapidly integrating new science into current practice
- Empowering patients to become value-conscious healthcare consumers

These are the building blocks advancing the practice of pharmacy. They are also the tools that can be used in a broader context to drive meaningful reform across all of healthcare.
SPOTLIGHT ON TREND
FOR 2008

UNIT COST
VS.
UTILIZATION
Looking back at 2008, you will gain insight into:

- **The key forces that shaped prescription drug trend in 2008.**
  Increased price inflation of branded pharmaceuticals and the growth of specialty drug spending were major drivers of unit costs in 2008.

- **Treatment areas that are emerging as the leading drivers of trend.**
  Utilization declined in many therapeutic areas due to emerging safety concerns, over-the-counter conversions, number of market withdrawals, and the launch of a limited number of new drugs.

2008 drug trend overview

The turbulent economic climate has refocused benefit plans and their members on lower-cost alternatives. In 2008, generic drugs remained a predominant form of therapy for prescription drug benefits; the average generic dispensing rate for Medco clients was 64.1%. Mail prescription volumes, which also offer benefit plans and members savings, increased for Medco clients.

The uncertain political environment also affected benefit plans and members. The potential change in and later election of a different political party has raised questions about the future funding, drug pricing, formulary design, and structure of benefit coverage for Medicare Part D enrollees.

One constant during this time of change was the slow rate of prescription-drug spending growth for Medco clients—an increase of 3.3%.* In 2008, the primary growth driver of trend shifted from utilization to unit cost. Increased price inflation of branded pharmaceuticals and the growth of specialty drug spending were major drivers of unit costs in 2008. Utilization growth declined in 2008. Several factors have played a role in decelerating the growth of prescription drug utilization, including the over-the-counter (OTC) conversion of the blockbuster drug Zyrtec®, safety concerns and withdrawals within several classes of drugs, and the launch of a limited number of new drugs, many of which were primarily indicated for low-prevalence conditions or did not represent major therapeutic gains.

* Reported trends are based on 2 years’ data on pharmaceutical spending and carriers with significant enrollment changes, an increase or decrease of greater than 50%, were not included in the analysis. This sample represents 77% of the $38.9 billion spent by Medco clients with integrated benefits (plans that include both retail and mail-order options for their members). Plan spending is reported on a per-eligible per-month basis, unless otherwise specified. Plan spending is the net cost to plan sponsors after discounts, rebates, subsidies, and member cost share have been applied. Drug trend is the percent change in plan spending from one year to the next.
KEY DRIVERS OF DRUG TREND

In 2008, drug trend for Medco’s book of business was 3.3%, an increase from 2.0% in 2007. Drug trend excluding specialty drugs was 1.3% in 2008.

The primary contributors to drug trend are utilization and unit cost.

Unit cost is the plan’s cost per unit of therapy. Unit costs grow if drug prices increase (“price inflation”) or if users move to higher-cost options within a therapeutic class, and unit costs decline if users move to lower-cost options within a therapeutic class (a change in “therapy mix”). For the analyses in this report, unit costs are expressed in terms of the net plan cost per day of therapy.

In 2008, unit costs increased 4.4%. Significant increases (over 8%) in the price inflation of branded pharmaceuticals and the growth in specialty drug spending due to introduction of new specialty drugs as well as the higher use of existing specialty drugs were the primary drivers of unit-cost growth.

Utilization is the amount of drugs obtained by plan members. Utilization increases if more members begin taking a drug (an increase in users) or if current users take more of the drug (an increase in days of use). For most of the analyses in this report, utilization is expressed in terms of the days of therapy per eligible (per household).

In 2008, utilization declined 1.1%. A number of factors have contributed to the deceleration of prescription drug utilization: OTC conversion of the blockbuster drug Zyrtec, safety concerns within several classes of drugs (e.g., osteoporosis drugs, hormone replacement therapy [HRT], and erythroid stimulants), the withdrawal of several cough and cold and migraine drugs, and the launch of a limited number of new drugs mainly for low-prevalence conditions.

UNIT COST VS. UTILIZATION

Unit cost

In 2008, unit costs grew 4.4%. This is a substantial increase from 2007, during which unit costs grew only 0.4%. The two primary drivers of unit-cost growth in 2008 were:

- The significant price inflation of branded pharmaceuticals, an average of 8% compared to generic drugs, which on average increased less than 1%.
- The rapid growth in specialty drug spending due to the recent introduction of several high-cost specialty drugs in 2007 and 2008, and the higher representation of specialty drug spending within total drug spending.

THERAPY MIX

First-in-class generics

First-time generic drug introductions from 2008 are shown in Table 1. A number of these were first in class. The combined U.S. market opportunity for all the new first-time generics approved in 2008 exceeded $11.6 billion. First-in-class generics were launched for the following therapeutic classes: osteoporosis, atypical antipsychotics, anticonvulsants, antidepressants, and migraine. Of particular note was the availability of first-time generics in the anticonvulsant class; three highly utilized anticonvulsants became available in generic form, and two more are scheduled to lose patent protection in 2009.

First-time generics reduce unit costs in their therapeutic classes, especially if they are released early in the year. In 2008, many of the generic introductions, including the first-in-class launches of many atypical antipsychotics, anticonvulsants, and migraine drugs, occurred late in the year. The late-in-the-year launch of these generics did not offset the increases in unit costs associated with branded pharmaceuticals.
Table 1. First-time generic drugs introduced during 2008
Source: U.S. Food and Drug Administration (FDA); IMS Health (retail sales)

<table>
<thead>
<tr>
<th>Generic approval</th>
<th>Brand name and dosage form</th>
<th>Generic name</th>
<th>Uses</th>
<th>Market sales in 2008 ($MM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1Q 2008</td>
<td>Fosamax®</td>
<td>alendronate tablets</td>
<td>Osteoporosis</td>
<td>Weekly: $1,415 Daily: $29</td>
</tr>
<tr>
<td>2Q 2008</td>
<td>Dovonex® Scalp</td>
<td>calcipotriene solution 0.005%</td>
<td>Psoriasis of the scalp</td>
<td>$163 (solution and cream)</td>
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<tr>
<td></td>
<td>Requip®</td>
<td>ropinirole</td>
<td>Parkinson’s disease, restless legs syndrome</td>
<td>$414</td>
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<tr>
<td></td>
<td>Yasmin®</td>
<td>drospirenone/ethinyl estradiol</td>
<td>Contraception</td>
<td>$609</td>
</tr>
<tr>
<td></td>
<td>Paxil CR®</td>
<td>paroxetine controlled-release tablets</td>
<td>Depression, panic, anxiety, premenstrual dysphoric disorder</td>
<td>$308</td>
</tr>
<tr>
<td></td>
<td>Wellbutrin XL® 150 mg</td>
<td>bupropion extended-release tablets</td>
<td>Depression</td>
<td>$898</td>
</tr>
<tr>
<td></td>
<td>Prilosec® 40 mg</td>
<td>omeprazole 40-mg capsules</td>
<td>Gastroesophageal reflux disease, ulcers</td>
<td>$168</td>
</tr>
<tr>
<td></td>
<td>Marinol®</td>
<td>dronabinol</td>
<td>Nausea, vomiting</td>
<td>$158</td>
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<tr>
<td>3Q 2008</td>
<td>Risperdal®</td>
<td>risperidone tablets and oral solution</td>
<td>Schizophrenia, bipolar disorder</td>
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<td>Lamictal®</td>
<td>lamotrigine</td>
<td>Seizures, bipolar disorder</td>
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<td>Depakote®</td>
<td>divalprox sodium</td>
<td>Seizures, bipolar disorder, migraine</td>
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<tr>
<td>4Q 2008</td>
<td>Cosopt®</td>
<td>dorzolamide/timolol ophthalmic solution</td>
<td>Glaucoma, ocular hypertension</td>
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<tr>
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<td>Keppra®</td>
<td>levetiracetam tablets</td>
<td>Seizures</td>
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<tr>
<td></td>
<td>Imitrex®</td>
<td>sumatriptan</td>
<td>Migraines</td>
<td>Tablets: $1,047 Injection: $199</td>
</tr>
<tr>
<td></td>
<td>Femara®</td>
<td>letrozole</td>
<td>Breast cancer</td>
<td>$316</td>
</tr>
</tbody>
</table>

Note: The table shows first-time generics launched in 2008 for brands with prior-year market sales greater than $125 million. FDA approval of a first-time generic may not align with market availability.

- Mylan’s generic paroxetine controlled-release product (Paxil CR) was approved on June 29, 2007. According to the company, Mylan settled patent litigation in October 2007, allowing it to launch its product no later than October 1, 2008. Mylan stated that it launched its generic with 180 days of exclusivity on two (12.5 mg and 25 mg) of the three strengths launched (also 37.5 mg).
- Teva announced the launch of generic bupropion extended-release 150-mg tablets June 2, 2008 (Wellbutrin XL 150 mg). Teva launched bupropion extended-release 300-mg tablets in December 2006. The generic versions of Wellbutrin XL 150-mg and 300-mg tablets received approval on December 14, 2006. Teva launched both the 150-mg and 300-mg bupropion extended-release tablets with 180-day exclusivity.
- Watson was awarded 180 days of marketing exclusivity for being the first to file an Abbreviated New Drug Application (ANDA) containing a paragraph IV certification for generic omeprazole 40-mg capsules (Prilosec 40 mg). Watson’s marketing exclusivity began upon commercial launch on July 25, 2008.
- Teva has launched their generic for Lamictal, which was approved by the FDA in August 2006. In February 2005, GlaxoSmithKline (GSK) and Teva entered into an agreement to settle patent litigation under which GSK granted Teva the exclusive right to manufacture and sell a generic version of Lamictal during the 6-month pediatric exclusivity, which ended on January 22, 2009.
- Hi-Tech and Apotex have shared 180-day exclusivity for generic dorzolamide (Cosopt and Trusopt®). Prasco will also be distributing authorized generics for these drugs.
- In October 2007, Mylan and UCB Pharma announced an agreement to settle pending litigation relating to Keppra tablets. Pursuant to the settlement, Mylan was given the right to market the 250-mg, 500-mg, and 750-mg strengths of levetiracetam tablets as early as November 1, 2008. Mylan’s generic was launched immediately and was the only one available until pediatric exclusivity expired on January 14, 2009.
- Spectrum entered into a settlement agreement with GSK that resolves U.S. patent litigation related to GSK’s Imitrex Injection. The confidential terms of the settlement permit Par to sell generic versions of certain sumatriptan injection products, with the launch occurring in November 2008. Dr. Reddy’s Laboratories launched an authorized generic for Imitrex tablets as the result of a patent litigation settlement. The first Orange Book patent expiration for Imitrex tablets occurred on February 6, 2009 (with a pediatric extension), final approval for their generic tablets has been granted.

The economic power of generics
For many plan sponsors, generic drugs remain the most valuable way to provide effective care to members while reducing plan costs. Generics offer the safety and efficacy of their brand-name counterparts at a significantly lower cost. The financial impact of a generic conversion is based on several market realities: first-time generics, lower prices, and low price inflation.
First-time generics. First-time generics offer three opportunities: as a generic equivalent for the specific brand-name drug, as a generic alternative for the other brand drugs in the same class, and as a possible generic substitution for brands in other therapeutic classes. For example, the availability of a generic for Imitrex® (sumatriptan) allows for generic substitution with sumatriptan products and also provides opportunities to use generic alternatives for other single-source triptans, such as Axert®.

Lower prices. Generic drugs generally cost 30% to 80% less than their brand-name counterparts. The price spread depends on a variety of factors, including the degree of market competition. During the first 6 months that a new generic drug is available, it may have only one manufacturer and the generic product will typically be priced closer to the brand. As more generic manufacturers enter the market, prices for the generic products tend to fall rapidly. If a large number of manufacturers enter the market, prices for the generics may drop 80% or more below the price of the brand.

Low price inflation. Drug price inflation is typically indexed by changes in the Average Wholesale Price (AWP). Prices for generic drugs increase more slowly than prices for brand-name drugs. In 2008, the average price inflation for generic drugs used by Medco members was only 0.5%, and unit costs for many generic drugs actually declined as market competition expanded. In contrast, the average price inflation for brand-name drugs was 8.4%.

The launch of a generic also offers plan sponsors an opportunity to translate the conversion into savings via efficient generic substitution. The introduction of generic versions of Fosamax® (alendronate sodium) at the beginning of 2008 illustrates the impact of a first-time generic on prescription volumes for a brand-name drug and a new generic (Figure 1). When generic alendronate sodium (Fosamax) was introduced in February 2008 and became the preferred choice by plan members, prescription volumes for the brand-name drug rapidly declined. During the first 30 days following launch of the generic products, the brand-name product lost 94% of its market share at mail and 84% of its market share at retail.

The transition to a new generic typically occurs more quickly at mail than at retail, largely because of the more focused and expansive use of generic substitution programs utilized for the mail-order pharmacy prescription processing. For example, within the first week after generic alendronate sodium (Fosamax) was introduced, the Medco mail-order pharmacy achieved a generic substitution rate of 93%, compared with a 63% substitution rate for the same period at retail.

Generic drugs account for the majority of prescriptions filled by plan members served by Medco. In 2008, the average annual generic dispensing rate (GDR) for Medco clients was 64.1%, compared with 59.7% in 2007 (Figure 2).
Plan incentives to shift therapy mix

The average level of generic drug utilization by plan members varies as a function of benefit plan design. Generic drug utilization can be affected by several factors, such as differences in formulary design, plan demographics, and the degree of management tool utilization to encourage members and physicians to select generic drugs.\(^5\)

A variety of approaches can be used to expedite the uptake of new generics. Plan management should be based on a comprehensive generics strategy that draws on a wide number of approaches to increase generic utilization rates.\(^6\) A comprehensive generics strategy can include:

| Plan design incentives to shift the therapy mix toward generic use | • Utilize management options that encourage the use of generics, such as:
|---|---|
| | • Offering temporary waivers of the co-payments that usually apply to the generic drugs
| | • Setting lower coinsurance or co-payment levels for generics than for brands
| | • Providing tiered co-payments linked to formulary status of high-cost brands
| Awareness of generic opportunities | • Notify members of specific generic opportunities, both for generic equivalents and alternatives
| | • Inform members of first-time generic introductions
| Formulary | • Develop programs based on a formulary that promotes generics along with preferred brands, including mailings about generic and brand-preferred alternatives to nonformulary drugs
| Member-pays-the-difference programs | • Make members responsible for their co-payments plus the difference in cost between the brand and its generic equivalent
| Coverage management | • Require clinical review of prescriptions for a nonpreferred drug before providing coverage; coverage may not be authorized if certain criteria are not met
THE GENERIC OPPORTUNITY SCORE

In order to reduce plan and member costs, an employer was looking for ways to impress on its diverse membership the benefits and cost savings associated with generic and mail utilization. Medco used the Generic Opportunity Score (GOS)* to identify potential opportunities for increasing generic utilization, including both generic equivalents and alternatives. The GOS is the percentage of prescriptions that are dispensed as generic when either generic equivalents or generic alternatives are available for brand-name drugs. Essentially it measures how much of the opportunity to use generics is being realized and how much remains in each category. GOS can be as high as 100% if all the potential opportunities for generic equivalents and alternatives are utilized.

Actions

Medco presented an employer with a GOS analysis of prescription data based on a 38,000-member population. The employer developed a strategy, based on this model, to derive both plan and member savings from greater utilization of generics. The employer's strategy revolved around Medco's brand-to-generic co-payment waiver program, which targeted the employer's members with opportunities to convert brand drugs to generics and/or obtain generics at mail. The program offered members a $0 co-payment for new generic prescriptions filled through Medco's mail-service pharmacy.

Results

The brand-to-generic co-payment waiver program achieved significant savings for the employer and members. Over 14% of the employer's population responded to the co-payment waiver communications, resulting in over 7,000 co-payment waivers applied. Twenty-five percent of the waivers were for brand prescriptions submitted as generics at mail, 40% were for generics at retail moved to mail, and 35% were for new generic prescriptions at mail.† The annual‡ impact of the co-payment waiver program resulted in a 1.2% increase in GOS, almost 22,500 generic prescriptions at mail, overall estimated annual savings of $1.8 million for the employer, and estimated annual savings of $300,000 for members.

*U.S. patent pending
†Annual estimated generic prescriptions at mail and estimated annual savings based upon initial waiver period performance and an 80% refill rate.
‡Existing prescriptions at mail for brands that became available as generics during the waiver period were not eligible to receive a co-payment waiver.

PRICE INFLATION OF BRANDED DRUGS

With a declining return on investment and a large number of blockbuster drugs facing imminent generic competition, the pharmaceutical industry is facing significant revenue challenges. Some of the forces eroding pharmaceutical return on investment include:

- Growing price competition from generics and me-too drugs (i.e., drugs that offer minimal benefits over similar drugs that have already been approved by the FDA)
- Payer changes in coverage policies
- A decline in the number of blockbuster drug introductions
- Fewer novel drugs reaching the market because of more stringent FDA approval criteria and requirements for Risk Evaluation and Mitigation Strategy programs
- A slowdown in drugs winning new labeled indications

Enhancing life-cycle management (LCM) strategies is one way that pharmaceutical companies are responding to these pressures. Although it may affect the utilization of a drug and/or its reimbursement status, strategic pricing is a common LCM strategy. It can entail launching novel drugs at a higher price and/or substantially increasing the cost of a single-branded pharmaceutical year-on-year. The practice of increasing the cost of a drug before its follow-on version is introduced has become more common because it makes the newer version appear financially advantageous compared with the older one, which is now available at a similar or higher cost.
In 2008, the inflation of branded pharmaceuticals used by plan members was a major contributor to the increase in unit costs. Over the last 5 years, the price inflation of branded drugs, including specialty drugs, has continued to increase while the price inflation of generic drugs has hovered at approximately 0.5% (Figure 3). During the past 5 years, increases in the price inflation of branded drugs greatly outpaced the overall price inflation of goods and services, as measured by the consumer price index for the same time period.

**GROWTH OF SPECIALTY DRUG SPENDING**

Unit-cost growth during 2008 was also driven by the number of new high-cost drugs that were approved in 2007 and 2008. In 2007 and 2008, about one-third of the new drug approvals were for high-cost specialty drugs used for the treatment of cancer, pulmonary arterial hypertension, and various immune-related or orphan conditions. Many of these drugs were chronically administered agents that cost tens of thousands of dollars per year. In addition, dosage creep or dosage increase may have also occurred among some of these specialty drugs. Although these new high-cost drugs are for small patient populations, their total cumulative use likely contributed to the rise in unit cost in 2008.

**Utilization**

In 2008, utilization growth declined by 1.1%. This is the first time in the last decade that overall drug utilization has declined. A number of factors are likely to have contributed to the moderate decline in utilization growth in 2008, including:

- Prescription (Rx)-to-OTC conversions of the blockbuster drug *Zyrtec* and *Miralax*®
- Safety concerns within several classes of drugs, including osteoporosis, HRT, and erythroid stimulants
- Market withdrawal of a several migraine and cough and cold medications
- The launch of a limited number of new drugs, many of which were indicated primarily for low-prevalence conditions
**USERS AND DAYS**

Utilization growth is a combination of two types of changes—changes in treatment rate (new users) and changes in treatment intensity (days per user).

- **Treatment rate** is a measure of the number of people who use drugs to treat a given condition.
- **Treatment intensity** is a measure of the average number of treatment days per year per user.

Drugs used to treat chronic conditions, such as hyperlipidemia, hypertension, and diabetes, showed small increases in treatment rate and intensity (Figure 4).

The treatment rate rapidly increased for antivirals, reflecting a greater number of users of miscellaneous antivirals such as Fampiclovir®, Tamiflu®, and Valtrex®. Although treatment intensity declined for selected biotechnology drugs, treatment rates increased dramatically for some products.

The treatment rates for hypnotics declined whereas treatment intensity increased, probably reflecting the shift to longer-term use of these drugs among patients who continue to use them.

**THE SWITCH FROM RX TO OTC**

Because of the increasing costs associated with developing new drugs and a declining number of drugs gaining regulatory approval each year, pharmaceutical companies actively utilize LCM strategies to augment existing franchise revenues or protect branded revenues from generic competition. Pharmaceutical companies continue to use the Rx-to-OTC model to maximize market share and revenues as a product nears the end of its patent life. In 2008, two therapeutic classes were affected by a drug gaining OTC approval.

**Allergy.** In late 2007, the FDA approved OTC sale of the allergy drug Zyrtec. As a result of this approval, utilization in the allergy prescription class declined by almost 30% in 2008.

**Gastrointestinal.** Miralax was approved for OTC sale late in 2006. However, although the branded version went OTC in 2006, the major generic equivalent prescription product did not exit the market until the FDA forced its removal late in 2007. As a result, the impact on utilization of gastrointestinal drugs was not evident until 2008. Utilization of prescription drugs in this category declined by over 9% in 2008.

**DRUG SAFETY**

Safety concerns reduced the utilization of drugs in the following therapeutic classes:

**Osteoporosis.** Data released during the latter part of 2008 raised new safety concerns about osteoporosis drugs. A study reported an association between osteonecrosis of the jaw and the use of osteoporosis drugs. In 2008, the utilization of these drugs declined almost 6%. Further decreases in utilization can be expected in 2009 because an FDA analysis released early this year reported a possible link between esophageal cancer and the use of osteoporosis drugs.
Hormone replacement therapy. The use of HRT has continued to decline since safety issues were identified by several studies beginning in 2002.12-14 Despite recent work suggesting that HRT can benefit a subset of the population, treatment rates declined 7% in 2008.15

Erythropoiesis-stimulating agents (ESAs). In 2008, the FDA issued a warning about the use of erythropoiesis-stimulating agents (ESAs), such as Epogen® and Aranesp®, for the prevention of chemotherapy-induced anemia in patients with cancer or chronic kidney failure. Data from several studies indicated that the use of ESAs by these patient populations could be associated with serious, potentially fatal side effects. The use of ESAs for this indication has been significantly curtailed.16

PRODUCT WITHDRAWALS
Utilization declined sharply for drugs in the migraine and cough and cold classes due to FDA-mandated market withdrawals. Typically there was a sharp increase in the remaining brands in the therapeutic category.

Migraine. The FDA issued warning letters to 20 companies in March of 2007 that were either producing or distributing ergotamine tartrate products.17 In 2008, utilization of this drug class decreased 1% while unit costs increased 7.1%.

Cough and cold. In mid-2007 the FDA began taking action against companies marketing products in timed-release dosage form that contain guaifenesin.18 In 2008, the removal of these products from the cough and cold class resulted in a sharp decline of 32% in use. The unit costs of the remaining single-source brands increased sharply by approximately 18%.

DRUG INNOVATION

New drugs
The FDA approved 21 new molecular entities (NMEs) and three new biologics in 200819-22 (Table 2). Two of these approvals were first-time treatments for the rare conditions of Huntington’s disease and cryopyrin-assisted periodic syndromes. Pharmaceutical companies will likely continue to focus on targeting niche disorders with a high unmet need, because new treatments for these types of disorders may garner a more favorable FDA review and they can be priced at a premium. The first-year impact of these new drugs on utilization was relatively small because some were introduced late in the year and many are indicated for low-prevalence conditions.

New indications
New indications approved during 2008 are shown in Table 3.23 Most of these drugs were not significant drivers of utilization growth in 2008.

ECONOMIC DOWNTURN
The recession has refocused benefit plans and their members on lower-cost alternatives. For example, more members are utilizing more generics. In 2008, the GDR for Medco’s clients increased—a 5% increase for mail prescription refills and a 4.3% increase for retail prescription fills. Mail-order volumes also increased for Medco clients.

It is also noteworthy that many benefit plans are encouraging the use of lower-cost alternatives by modifying plan designs. For example, members with plan designs* employing:

• Step therapy and quantity management rules increased by 16.5%
• Dispensing quantity rules increased by almost 9%
• Prior authorization rules increased by 1.5%

The increased use of generics and the shift to mail order suggests that members are taking greater advantage of the cost savings associated with mail order and generics and that benefit plans are increasingly promoting the use of these programs.

* The analysis of benefit plan design is based on 2 years’ claim data for approximately 21 million members in commercial plans managed by Medco.
Table 2. New drug and biologic introductions in 2008
Source: "The Pink Sheet" 17-18 and U.S. Food and Drug Administration19-20

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Brand name</th>
<th>Generic name</th>
<th>Type</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1Q 2008</td>
<td>Intelence™*</td>
<td>etravirine</td>
<td>NME</td>
<td>HIV infection as second-line therapy</td>
</tr>
<tr>
<td></td>
<td>Recothrom®</td>
<td>thrombin (recombinant)</td>
<td>B</td>
<td>Aid to hemostasis</td>
</tr>
<tr>
<td></td>
<td>Xyntha®</td>
<td>antithrombin factor (recombinant), plasma/albumin free</td>
<td>B</td>
<td>Prevention of bleeding in hemophilia A</td>
</tr>
<tr>
<td></td>
<td>Arcalyst™*</td>
<td>rilonacept</td>
<td>TB</td>
<td>Cryopyrin-associated periodic syndromes disorders</td>
</tr>
<tr>
<td></td>
<td>Artiss®</td>
<td>fibrin sealant (human)</td>
<td>B</td>
<td>For adhering autologous skin grafts to surgically prepared wound beds</td>
</tr>
<tr>
<td></td>
<td>Pristiq®</td>
<td>desvenlafaxine</td>
<td>NME</td>
<td>Major depressive disorder</td>
</tr>
<tr>
<td></td>
<td>Treanda™*</td>
<td>bendamustine injection</td>
<td>NME</td>
<td>Chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>2Q 2008</td>
<td>Rotarix®</td>
<td>rotavirus vaccine, live, oral</td>
<td>B</td>
<td>Prevention of rotavirus gastroenteritis</td>
</tr>
<tr>
<td></td>
<td>Cimzia®</td>
<td>certolizumab pegol injection</td>
<td>TB</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td></td>
<td>Relistor®</td>
<td>methylnaltrexone injection</td>
<td>NME</td>
<td>Opioid-induced constipation</td>
</tr>
<tr>
<td></td>
<td>Entereg®</td>
<td>alvimopan</td>
<td>NME</td>
<td>Acceleration of gastrointestinal recovery after surgery</td>
</tr>
<tr>
<td></td>
<td>Pentace®</td>
<td>diphtheria, tetanus, and acellular pertussis (DTaP), poliovirus, haemophilus b vaccine</td>
<td>B</td>
<td>Immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to H influenzae type b</td>
</tr>
<tr>
<td></td>
<td>Kinrix™</td>
<td>DTaP, polio vaccination</td>
<td>B</td>
<td>Immunization against diphtheria, tetanus, pertussis, and poliomyelitis</td>
</tr>
<tr>
<td></td>
<td>Durezol™*</td>
<td>difluprednate ophthalmic emulsion</td>
<td>NME</td>
<td>Postoperative ocular inflammation and pain</td>
</tr>
<tr>
<td>3Q 2008</td>
<td>Clevidprex™</td>
<td>clevidipine butyrate injection</td>
<td>NME</td>
<td>High blood pressure when oral therapy cannot be used</td>
</tr>
<tr>
<td></td>
<td>Xenazine®*</td>
<td>tetrabenazine</td>
<td>NME</td>
<td>Chorea of Huntington’s disease</td>
</tr>
<tr>
<td></td>
<td>Nplate®</td>
<td>romiplostim injection</td>
<td>TB</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>4Q 2008</td>
<td>Rapaflo®</td>
<td>silodosin</td>
<td>NME</td>
<td>Benign prostatic hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Cinryze®</td>
<td>Cs inhibitor (human) injection</td>
<td>B</td>
<td>Hereditary angioedema</td>
</tr>
<tr>
<td></td>
<td>Vimpat®</td>
<td>lacosamide</td>
<td>NME</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Toviaz®</td>
<td>fesoterodine extended-release</td>
<td>NME</td>
<td>Overactive bladder</td>
</tr>
<tr>
<td></td>
<td>Banzel™</td>
<td>rufinamide</td>
<td>NME</td>
<td>Lennox-Gastaut syndrome</td>
</tr>
<tr>
<td></td>
<td>Promacta®*</td>
<td>eltrombopag</td>
<td>NME</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>tapentadol</td>
<td>tapentadol</td>
<td>NME</td>
<td>Moderate to severe acute pain</td>
</tr>
<tr>
<td></td>
<td>Luscedra™</td>
<td>fospropofol injection</td>
<td>NME</td>
<td>Sedative-hypnotic agent</td>
</tr>
<tr>
<td></td>
<td>Mozobil™*</td>
<td>plerixafor</td>
<td>NME</td>
<td>Hematopoietic stem cell transplant</td>
</tr>
<tr>
<td></td>
<td>degarelix</td>
<td>degarelix</td>
<td>NME</td>
<td>Prostate cancer</td>
</tr>
</tbody>
</table>

Note: The table shows new prescription drugs approved by the FDA during 2008. This list does not include NME diagnostic agents. Three types of new drugs are shown:
NME: New molecular entity
B: Biologic (approved by the Center for Biologics Evaluation and Research)
TB: Therapeutic biologic (approved by the Center for Drug Evaluation and Research)

Bold text indicates specialty drugs.

*Priority review

a After FDA approval, tapentadol required review by the U.S. Drug Enforcement Agency for scheduling; this review delayed launch until a scheduling classification was determined.

b Potential trade names for degarelix are still under review with the FDA. After issuing a trade name, Ferring Pharmaceuticals will immediately begin marketing the brand in the United States.
Table 3. New indications approved in 2008
Source: U.S. Food and Drug Administration*

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Brand name</th>
<th>Generic name</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1Q 2008</td>
<td>Cialis®</td>
<td>tadalafil</td>
<td>Once-daily treatment of erectile dysfunction</td>
</tr>
<tr>
<td></td>
<td>Tysabri®</td>
<td>natalizumab injection</td>
<td>Treatment of Crohn’s disease</td>
</tr>
<tr>
<td></td>
<td>WelChol®</td>
<td>colesuvelam</td>
<td>Improvement in glycemic control in type 2 diabetes</td>
</tr>
<tr>
<td></td>
<td>Humira®</td>
<td>adalimumab injection</td>
<td>Treatment of plaque psoriasis and treatment of active juvenile idiopathic arthritis</td>
</tr>
<tr>
<td></td>
<td>Aloxi®</td>
<td>palonosetron injection</td>
<td>Prevention of postoperative nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td>Avastin®</td>
<td>bevacizumab injection</td>
<td>Treatment of metastatic breast cancer in combination with paclitaxel</td>
</tr>
<tr>
<td></td>
<td>Janumet®</td>
<td>metformin/sitagliptin</td>
<td>Initial treatment of type 2 diabetes</td>
</tr>
<tr>
<td>2Q 2008</td>
<td>Vyvanse®</td>
<td>lisdexamfetamine dimesylate</td>
<td>Treatment of attention-deficit hyperactivity disorder (ADHD) in adults</td>
</tr>
<tr>
<td></td>
<td>Amitiza®</td>
<td>lubiprostone</td>
<td>Treatment of irritable bowel syndrome with constipation in women</td>
</tr>
<tr>
<td></td>
<td>Abilify®</td>
<td>aripiprazole</td>
<td>Treatment of bipolar I disorder</td>
</tr>
<tr>
<td></td>
<td>Strattera®</td>
<td>atomoxetine</td>
<td>Maintenance treatment of attention-deficit hyperactivity disorder</td>
</tr>
<tr>
<td></td>
<td>Genotropin®</td>
<td>somatropin injection</td>
<td>Treatment of idiopathic short stature</td>
</tr>
<tr>
<td></td>
<td>Orencia®</td>
<td>abatacept injection</td>
<td>Treatment of active juvenile idiopathic arthritis</td>
</tr>
<tr>
<td></td>
<td>Cymbalta®</td>
<td>duloxetine</td>
<td>Treatment of fibromyalgia-induced pain</td>
</tr>
<tr>
<td></td>
<td>Avodart®</td>
<td>dutasteride</td>
<td>In combination with tamulosin, treatment of symptomatic benign prostatic hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Velcade®</td>
<td>bortezomib injection</td>
<td>First-line treatment of multiple myeloma</td>
</tr>
<tr>
<td></td>
<td>Concerta®</td>
<td>methylphenidate</td>
<td>Treatment of ADHD in adults</td>
</tr>
<tr>
<td></td>
<td>Exforge®</td>
<td>amlodipine/valsartan</td>
<td>First-line treatment of high blood pressure</td>
</tr>
<tr>
<td></td>
<td>Diovan® HCT</td>
<td>valsartan/valsartan</td>
<td>First-line treatment of high blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hydrochlorothiazide</td>
<td></td>
</tr>
<tr>
<td>3Q 2008</td>
<td>Viread®</td>
<td>tenofovir disoproxil fumarate</td>
<td>Treatment of chronic hepatitis B</td>
</tr>
<tr>
<td></td>
<td>Valtrex®</td>
<td>valacyclovir</td>
<td>Treatment of chickenpox in patients 2 to 18 years of age</td>
</tr>
<tr>
<td></td>
<td>Gardasil®</td>
<td>human papillomavirus (HPV) vaccine</td>
<td>Prevention of cervical, vulvar, and vaginal cancer and genital warts</td>
</tr>
<tr>
<td></td>
<td>Gamunex®</td>
<td>immune globulin, intravenous</td>
<td>Treatment of chronic inflammatory demyelinating polyneuropathy</td>
</tr>
<tr>
<td></td>
<td>Alimta®</td>
<td>pemetrexed</td>
<td>Initial treatment of nonsquamous non-small cell lung cancer</td>
</tr>
<tr>
<td></td>
<td>Kogenate® FS</td>
<td>antihemophilic factor</td>
<td>Treatment of pediatric hemophilia A to reduce the risk of joint damage</td>
</tr>
<tr>
<td></td>
<td>Seroquel XR®</td>
<td>quetiapine extended-release</td>
<td>Acute and maintenance treatment of bipolar I disorder</td>
</tr>
<tr>
<td>4Q 2008</td>
<td>Treanda®</td>
<td>bendamustine injection</td>
<td>Treatment of indolent B-cell non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td></td>
<td>Crestor®</td>
<td>rosvastatin</td>
<td>Treatment of primary dysbetalipoproteinemia (Fredrickson type III hyperlipoproteinemia)</td>
</tr>
<tr>
<td></td>
<td>Norditropin®</td>
<td>somatropin injection</td>
<td>Treatment of short stature in children born small for gestational age</td>
</tr>
<tr>
<td></td>
<td>Ranexa®</td>
<td>ranolazine</td>
<td>First-line treatment of chronic angina</td>
</tr>
<tr>
<td></td>
<td>Boniva®</td>
<td>ibandronate</td>
<td>Prevention of postmenopausal osteoporosis</td>
</tr>
<tr>
<td></td>
<td>PEG-Intron® + Rebetol®</td>
<td>peginterferon alfa-2b and ribavirin</td>
<td>Treatment of pediatric hepatitis C</td>
</tr>
<tr>
<td></td>
<td>Reclast®</td>
<td>zoledronic acid injection</td>
<td>Treatment of osteoporosis in men</td>
</tr>
<tr>
<td></td>
<td>Gleevac®</td>
<td>imatinib</td>
<td>Use after resection of Kit positive gastrointestinal stromal tumors</td>
</tr>
</tbody>
</table>

Note: The table shows some of the efficacy supplements approved by the FDA during 2008. *Consult product label for the exact wording of the indications for these products. Bold text indicates specialty drugs.
Drug trend drivers and moderators

Three broad therapeutic categories, central nervous system (CNS), cardiovascular, and gastroenterology, contributed to approximately half of all drug spending in 2008 (Figure 5). Also contributing significantly were drugs from the endocrine and diabetes, respiratory, anti-infectives, and musculoskeletal and rheumatology therapeutic categories.

Figure 5. Top therapeutic categories contributing to drug spending in 2008
Source: Medco data

Note: The figure shows the percent contribution of each therapeutic category to overall plan cost in 2008.

Figure 6. Top 10 trend drivers in 2008
Source: Medco data

Note: This figure shows the contribution of the top 10 therapeutic classes to overall trend in 2008. Therapeutic classes are rank-ordered from the largest positive contributor (at the top) to the smallest positive contributor (at the bottom). The figure also shows the year-over-year changes for plan cost (drug trend), utilization (days per eligible), and unit cost (cost per day) for these 10 classes. Spending growth factors multiply to yield total trend, so utilization growth and unit-cost growth may not be additive. *Includes treatments for Alzheimer’s and Parkinson’s diseases.
TOP 10 TREND DRIVERS

The 10 therapeutic classes that had the largest impact on trend are shown in Figure 6. Spending increased for all these therapeutic classes, but spending declines for lipid-lowering drugs and allergy drugs helped to moderate the overall trend.

1. Diabetes therapy

Plan cost*: 7.2%  Trend: 8.6%
Treatments: Type 1 and type 2 diabetes
This class includes insulin products, noninsulin hypoglycemic drugs, blood glucose-monitoring equipment, and other supplies.

For the second year, diabetes drugs were the most powerful driver of trend. Utilization growth remained moderate, but the unit costs of treatment continued to increase. Price inflation for brand-name products and a shift in treatment mix toward newer, more expensive products in the category, such as Januvia®, continued to drive unit-cost growth for this therapeutic class. Achieving glycemic control in patients with diabetes often requires use of several agents in combination.

Utilization: 0.3%
- Greater use of newer insulin therapies, including Lantus SoloSTAR®, NovoLog®, and Levemir® contributed to a moderate increase in utilization.
- Utilization growth of newer insulin therapies and other oral agents (e.g., Januvia) offset the continuing decline in Avandia® utilization that occurred after safety concerns were raised about the increased risk of heart problems among users of the drug.24
- Utilization growth for noninsulin oral hypoglycemic drugs was led by Janumet® and Januvia.
- Utilization growth also increased for metformin, which is likely due to its recommended use as a first-line therapy.
- Utilization of Byetta® has declined moderately because of the potential link to pancreatitis associated with its use.

Unit Cost: 8.3%
- Unit-cost growth for insulin therapies was led by Lantus, Lantus SoloSTAR, NovoLog, and Levemir. Noninsulin oral hypoglycemic unit-cost growth was driven by increased use of Janumet and Januvia.

2. Rheumatological drugs

Plan cost: 3.4%  Trend: 17.2%
Treatments: Rheumatoid arthritis (RA), plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and other autoimmune conditions

Trend was robust for the biologics in the rheumatological category in 2008, driven by both increased utilization and unit-cost growth of newer, more expensive specialty drugs.

Utilization: 9.7%
- Utilization growth was particularly strong for the biologic Humira®, approved for the additional indications of chronic plaque psoriasis and juvenile RA in 2008 and for Crohn's disease in 2007.
- Utilization increased moderately for Enbrel®.

Unit Cost: 6.9%
- Unit costs grew substantially for Enbrel and increased moderately for Humira.

*As a percentage of total plan spending (i.e., the net cost to plan sponsors after discounts, rebates, subsidies, and member cost share have been applied) in 2008.
3. Seizure drugs
Plan cost: 4.0%  Trend: 13.9%
Treatments: Epilepsy, neuropathic pain, psychiatric disorders

Utilization growth increased for anticonvulsants because of the continuing expansion of indications for these drugs, such as bipolar depression, neuropathic pain, and fibromyalgia. For example, Lyrica® was approved for treating fibromyalgia in 2007. Generic versions of Trileptal®, Lamictal®, Keppra®, and Depakote® became available from late 2007 through 2008, thereby making the anticonvulsant drug class predominantly generic. This pattern will be further extended if the blockbuster drug Topamax® goes generic, as expected, in early 2009.

Given that seizure drugs have been a trend driver for many years and that drugs in this class, which have combined sales well in excess of $6 billion per year, have fallen to generic competition, it is likely that unit-cost growth will decline in the coming years.

Utilization: 6.1%
- Utilization growth was especially strong for gabapentin and Lyrica.
- Growth was also seen for Topamax and for Keppra and its generics.

Unit Cost: 7.4%
- Unit-cost growth increased sharply for Lyrica.

4. Antiviral drugs
Plan cost: 3.4%  Trend: 16.0%
Treatments: Influenza, hepatitis, herpes, HIV/AIDS

Spending growth for HIV/AIDS therapies and miscellaneous antiviral drugs continued to grow rapidly in 2008. Trend was driven by increased unit-cost growth for HIV/AIDS therapies and increased utilization growth for miscellaneous antivirals.

Utilization: 8.7%
- Utilization growth for HIV/AIDS therapies increased for Atripla®, Isentress®, and Truvada®.
- Increased utilization growth of miscellaneous antivirals, such as Famciclovir, Tamiflu, and Valtrex, drove utilization growth for this drug class.

Unit Cost: 6.7%
- Unit-cost growth was particularly strong for several HIV/AIDS therapies, including Atripla and Truvada.
- Unit-costs increased moderately for the miscellaneous antiviral Famciclovir.

5. Cancer and transplant drugs
Plan cost: 4.1%  Trend: 11.8%
Treatments: This category includes antineoplastics, immunosuppressants, antimetabolites, hormone therapies, and molecular target inhibitors that are used in cancer and transplant treatments.

Unit cost was the primary driver of spending growth for this therapeutic class. The robust increase in unit cost was due to the continued shift in therapy mix to more expensive, single-source, orally administered specialty drugs that are taken for a longer period of time than cytotoxic chemotherapies.
Utilization: 0.2%
- The moderate increase in the utilization growth of cancer and transplant drugs was largely due to an increase in the number of users.

Unit Cost: 11.6%
- Rapid unit-cost growth was driven by:
  - Brand-name targeted cancer treatments such as Revlimid®, Gleevec®, and Sutent®
  - The immunosuppressant drug Cellcept®
  - The aromatase inhibitors Arimidex® and Femara®

6. Selected neurological drugs
Plan cost: 2.4%  Trend: 175%
Treatments: Alzheimer’s disease, Parkinson’s disease, multiple sclerosis (MS)

Spending growth for selected neurological drugs grew rapidly in 2008 because of the increased use of drugs to treat both Parkinson’s disease and Alzheimer’s disease and the large unit-cost growth for all drugs in this category. Although Requip®, an antiparkinsonian agent, became available in generic form, its introduction did not significantly help to offset price increases for the leading brand-name drugs.

Utilization: 5.1%
- Utilization increased for the antiparkinsonian drug Mirapex.
- Utilization also increased for some of the drugs used to treat Alzheimer’s disease, including Namenda®, Aricept®, and Exelon®.
- Utilization was essentially unchanged for drugs used to treat MS.

Unit Cost: 11.8%
- Unit costs grew rapidly for Copaxone® and more moderately for Tysabri®.

7. Anticoagulant and antiplatelet drugs
Plan cost: 2.9%  Trend: 14.0%
Treatments: Reduction in clot formation or clot enlargement. There are three categories of anticoagulant drugs: inhibitors of clotting-factor synthesis, inhibitors of thrombin, and antiplatelet drugs.

The anticoagulant and antiplatelet therapeutic class did not appear on the list of top 10 trend drivers for 2007 but returned to the list in 2008 as a major driver, in large part because of the court ruling that upheld the patent for Plavix®, resulting in the market withdrawal of the generic version of Plavix.

Utilization: 0.4%
- Utilization of Plavix increased rapidly after a court ruling upheld the patent for this drug.
- Utilization of Aggrenox® increased moderately.
- Utilization growth was also driven by moderate cost increases in low-molecular-weight heparin drugs, including Lovenox®, Fragmin®, and Arixtra®.

Unit Cost: 13.5%
- The rapid increase in unit-cost growth was driven largely by the absence of generic for Plavix.
- Unit costs increased moderately for the antiplatelet drug Aggrenox and for the heparin drugs Lovenox and Fragmin.
8. Urological
Plan cost: 2.5%  Trend: 15.8%
Treatments: Overactive bladder, erectile dysfunction, benign prostatic hypertrophy (BPH), bladder pain

Spending growth for urological drugs was driven largely by increases in unit costs for single-source brand-name drugs. There are now a large number of drugs for the treatment of overactive bladder.

Utilization: 3.4%
• Utilization growth increased for drugs used to treat BPH, including Uroxatral®, Avodart®, finasteride, and Flomax®.
• Vescicare®, used to treat bladder pain and discomfort, showed a relatively small increase in use.
• Utilization for erectile dysfunction drugs did not change except for a small increase in the use of Cialis®.

Unit Cost: 12.0%
• Unit-cost growth accelerated for multiple drugs in this class, including Flomax, Vescicare, Cialis, and Viagra®.

9. Respiratory drugs
Plan cost: 5.9%  Trend: 6.0%
Treatments: Asthma, chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension

Spending growth for respiratory drugs was largely driven by increased unit-cost growth for new asthma drugs employing hydrofluoroalkane (HFA) as the propellant.

Utilization: -2.1%
• Utilization growth of beta-agonist inhalers remained relatively constant as use shifted from Albuterol® to ProAir® HFA and Proventil® HFA.
• Utilization of the inhaled corticosteroid Pulmicort Flexhaler® increased moderately.

Unit Cost: 8.3%
• Unit-cost growth accelerated for:
  - ProAir HFA and Proventil HFA
  - Pulmicort Flexhaler

10. Antipsychotic drugs
Plan cost: 2.4%  Trend: 15.3%
Treatments: Schizophrenia, bipolar disorder, and other psychiatric disorders

Despite safety concerns for the elderly and children, utilization of antipsychotic drugs increased sharply.16, 27 Expanded indications for Abilify® (i.e., schizophrenia in adolescents, adjunctive therapy in adult and pediatric patients with bipolar mania, pediatric bipolar mania) also drove the strong growth in utilization of this class.28 Although the generic conversion of Risperdal® occurred in the latter part of 2008, price inflation of single-source drugs still drove increases in unit-cost growth.

Utilization: 4.3%
• Utilization growth was led by Seroquel XR®, Seroquel®, and Abilify®.

Unit Cost: 10.5%
• Seroquel XR and Seroquel contributed to the sharp increase in unit-cost growth.
TRENDS MODERATORS

Two therapeutic classes—lipid-lowering and allergy drugs—were major decelerators of trend in 2008 (Figure 7).

1. Lipid-lowering drugs
   - Plan cost: 9.8%  Trend: -4.7%
   - Treatments: Cholesterol and triglyceride management. This class includes statins, fibrates, cholesterol absorption inhibitors, and niacin products.

In spite of continued growth in utilization, lipid-lowering drugs were a leading trend reducer for the second year in a row because of the introduction of generics in the class and a continued shift to these products. The increased use of lipid-lowering drugs can be attributed to several factors. Among them are:

- Expansion of clinical guidelines that significantly expand the eligible population for cholesterol-lowering therapy.19, 20
- Recent clinical studies supporting more aggressive cholesterol lowering for some patients and, in some cases, the use of multiple agents.29-34
- Increased prevalence and detection of high lipid levels

The generic conversions of two blockbuster statin drugs in 2006, Pravachol® (pravastatin) and Zocor® (simvastatin), have shifted the therapy mix toward the use of generics in this class, moderating the trend for this drug class.

Utilization: 1.4%
- Utilization for lipid-lowering statin drugs increased moderately.
- Utilization growth for Vytorin® decreased because of safety concerns, which likely further shifted the therapy mix to generics.
- Utilization increased for the prescription version of the omega-3 fatty acid Lovaza®.

Unit Cost: -6.0%
- Unit costs for lipid-lowering drugs decelerated for the second year in a row as the cost savings associated with generic pravastatin (Pravachol) and simvastatin (Zocor) continued.
- A shift in therapy mix toward generic simvastatin (Zocor) drove savings in unit costs.

2. Allergy
   - Plan cost: 1.7%  Trend: -35.4%
   - Treatments: Prevent or relieve indoor and outdoor allergens

In 2008, the antihistamine Zyrtec transitioned from a prescription drug to an OTC drug. This switch significantly decelerated spending for the entire allergy category.
Utilization: -29.8%
• Utilization dropped sharply because Zyrtec was converted to OTC status and was no longer covered by most plans.
• Use also moderately declined for fexofenadine HCl and Clarinex® as members likely turned to OTC options.

Unit Cost: -8.1%
• Unit-cost growth dropped for most allergy drugs; fexofenadine HCl had the largest declines.

TREND WATCH: FAST AND SLOW MOVERS

Fast movers
In addition to the top 10 trend drivers, four therapeutic classes showed robust spending growth in 2008 (Table 4). Although these “fast movers” correspond to a small percentage of overall spending, their fast growth makes them important trend drivers to watch and manage closely.

Among the fast movers, two classes stand out. The trend for narcotic analgesics, driven almost exclusively by unit-cost growth, increased by almost 9%. The loss of generics for OxyContin® during 2008 undoubtedly contributed to this fast growth. Drugs used to treat attention-deficit hyperactivity disorder (ADHD) also showed rapid growth in both utilization and unit costs during 2008. Rising use of these agents to treat adult ADHD likely accounts for part of this growth.

Slow movers
Also of note are three therapeutic classes that showed significant spending decreases, which helped to moderate trend in 2009. These “slow movers” showed modest spending growth or a small spending decline (Table 4).

Antihypertensive drugs were a trend moderator during 2008. This group of drugs has experienced robust utilization, and entry of numerous generics in this class in 2007 and 2008 helped to push trend down by almost 5% in 2008.

Table 4. Additional trend drivers with rapid or slow growth in 2008
Source: Medco data

<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>Plan cost (%)</th>
<th>Trend (%)</th>
<th>Utilization (% growth)</th>
<th>Unit cost (% growth)</th>
<th>Key events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast movers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>2.1</td>
<td>16.3</td>
<td>5.8</td>
<td>10.0</td>
<td>Increased unit costs and utilization of Vyvanse®.</td>
</tr>
<tr>
<td>Selected biotechnology</td>
<td>3.5</td>
<td>8.8</td>
<td>-1.2</td>
<td>10.1</td>
<td>Increased unit costs for interferon treatments (Rebif®, Avonex®, and Nordiflex®).</td>
</tr>
<tr>
<td>Narcotic pain relief</td>
<td>3.0</td>
<td>7.9</td>
<td>4.4</td>
<td>3.3</td>
<td>Increased treatment durations for OxyContin®.</td>
</tr>
<tr>
<td>Selected hormones</td>
<td>1.4</td>
<td>18.0</td>
<td>2.3</td>
<td>15.3</td>
<td>Increased unit costs for androgens (e.g., Androgel® and Testim®) and several miscellaneous agents, including Sensipar®, Kuvan®, and Zemplar®.</td>
</tr>
<tr>
<td>Slow movers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>7.5</td>
<td>-3.8</td>
<td>-0.4</td>
<td>-3.5</td>
<td>Unit-cost declines in categories dominated by generics: angiotensin-converting enzyme (ACE) inhibitors and beta-blockers. Continued savings from the generic conversions of Toprol-XL®, Norvasc®, Lotrel®, and Coreg®.</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>5.3</td>
<td>-0.2</td>
<td>-0.2</td>
<td>0.0</td>
<td>Increase in treatment rates. Flat unit-cost growth because of many generics.</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>3.0</td>
<td>-0.3</td>
<td>-1.5</td>
<td>1.2</td>
<td>Decreased treatment rates because of continuing concerns about resistance. Decreased utilization of Omnicef®. Increased unit-cost growth and utilization for cefdinir.</td>
</tr>
</tbody>
</table>
Specialty healthcare

Specialty drugs are now available to treat a wide variety of complex conditions, such as cancer, growth hormone deficiency, hemophilia, HIV, hepatitis, infertility, MS, metabolic disorders, chemotherapy-induced neutropenia, age-related macular degeneration, osteoporosis, pulmonary arterial hypertension, and RA. Many specialty drugs are administered via infusion or self-injection and typically require special handling and specialized patient support. In 2008, several new specialty drugs were introduced (Table 2) and a number of specialty drugs received approval for new or expanded indications.

THE SPECIALTY DOLLAR

Although they generate relatively small prescription volumes, specialty drugs represent a significant component of pharmacy spending and are a major driver of spending growth. The annual cost of a specialty drug to treat a complex chronic condition can range from $6,000 to more than $400,000 per year.35

Specialty drugs are typically covered under both the pharmacy and medical benefits. The allocation of a specialty drug to either pharmacy or benefit plan coverage varies greatly among plan sponsors—40% to 70% of specialty drugs can be billed under the medical benefit. In general, drugs that can be self-administered are usually billed under the pharmacy benefit, whereas drugs requiring infusion are usually billed under the medical plan.

The costs reported here are for specialty drugs that were purchased under the pharmacy benefit. For drugs billed under the medical plan, information on cost and utilization is often difficult to retrieve and analyze because of the imprecision of the drug codes used in medical billing.

SPECIALTY DRUG SPENDING GROWTH

Specialty drug spending is growing rapidly for many plans. For Medco clients, specialty drugs accounted for 12.8% of total pharmacy spending in 2008, up from 11.4% in 2007. There are at least three reasons for this increase:

- Many specialty drugs are protein-based products and there is currently no pathway for approval of generic protein-based generics that are approved under the Public Health Services Act.
- A large portion of new drug approvals are in the specialty category. As a result, this drug category is being affected by many high-cost introductions.
- Drugs are shifting from coverage under the medical benefit to under the pharmacy benefit.

SPECIALTY TREND DRIVERS

In 2008, spending for specialty drugs covered under the pharmacy benefit continued to rise sharply. Specialty spending grew 15.8% in 2008, an increase from the 12.4% growth rate in 2007.

Unit cost growth

In 2008, unit cost growth for specialty drugs increased 11.5%. Several factors that contributed to the increase in unit costs for specialty drugs include:

- Price inflation of specialty drugs
- A significant proportion of new drug approvals in 2007 and 2008 for high-cost specialty drugs
- Dosage creep or dosage increase among some specialty drugs
Utilization growth

Utilization of specialty drugs increased 4.3% in 2008, far exceeding the average utilization decline of 1.1% for the overall book of business. Utilization growth was driven primarily by:

- Increasing use of tumor necrosis factor inhibitors, such as Enbrel and Humira.
- Increasing number of treatment options for pulmonary arterial hypertension (PAH). Although there is no cure for PAH, there are many more treatment options, such as Remodulin®, Tracleer®, Letairis®, Revatio®, and Ventavis®, that can be used to help relieve the symptoms of the disease. Also, the use of these drugs in combination is not uncommon.
- Reallocation of some specialty drugs from coverage under the medical to the pharmacy benefits.
- Increased use of specialty drugs for new indications such as psoriasis.

The growth in pharmacy spending for specialty drugs was concentrated in a small number of therapeutic areas (Figure 8). Spending increases were highest for drugs used to treat RA and other autoimmune disorders, psoriasis, MS, and cancer.

Figure 8. Top therapeutic classes contributing to pharmacy spending for specialty drugs in 2008

Source: Medco data

Note: The figure shows the percent contribution of each therapeutic class to pharmacy spending for specialty drugs in 2008.

* Treatments for RA, plaque psoriasis, Crohn’s disease, ankylosing spondylitis, and other autoimmune conditions

TOP SPECIALTY TREND DRIVERS

Growth rates for the top drivers of specialty trend are shown in Figure 9. For some specialty drug classes, such as rheumatological, pulmonary arterial hypertension and anticoagulation, utilization growth was the primary contributor to trend. For other classes or categories, such as cancer and MS, increased unit costs were the primary driver of trend.

SPECIALTY TREND MODERATORS

Two specialty drug classes—anemia and hepatitis C—showed significant spending declines in 2008, moderating the overall growth rate for this class (Figure 9). Utilization of anemia treatments declined after the release of an FDA public health advisory on these products (Aranesp®, Epogen®, and Procrit®). Utilization decline for the hepatitis C class likely reflects the success rates with current best therapy, which includes a pegylated interferon and ribavirin, and the fact that retreatment is not currently recommended for patients for whom this therapy fails. Pegylated interferon plus ribavirin can cure 40% to 50% of patients who complete the recommended duration of therapy.
Specialty drugs were a significant component of trend within several of the top 10 trend-driving categories, including respiratory, cancer, and rheumatological drugs (Figure 10).

**Rheumatological.** Specialty treatments for RA (such as *Enbrel* and *Humira*) were the primary drivers of trend for this therapeutic category. These drugs are also used for a variety of other immunological diseases, and the cost for treating these diseases also appears in the rheumatology category.

**Cancer and transplant.** Spending growth was driven by price inflation for single-source brands and a shift in therapy mix toward new, more targeted therapies.

**Select neurological.** Spending growth was dominated by specialty treatments for MS (e.g., *Copaxone*, *Tysabri*).

**Anticoagulant and antiplatelet.** Low-molecular-weight heparins, such as *Lovenox*, are specialty drugs within the anticoagulant class. These high-cost drugs are used to prevent and treat thromboembolism.

**Respiratory.** The respiratory category includes several high-cost specialty drugs to treat pulmonary arterial hypertension, such as *Revatio*, *Tracleer*, *Letaris*, and *Ventavis*, as well as *Xolair*, which is used in the treatment of asthma.

### Medicare trend

The passage of the Medicare Modernization Act of 2003, including the launch of Medicare Part D, has both increased access to drugs for persons aged 65 or older and changed the manner in which retiree prescription drug benefits are funded.

As of February 2009, there were 45.2 million elderly and disabled retirees eligible for Medicare Part D and 26.7 million beneficiaries enrolled. The number of eligible recipients is expected to increase dramatically over the next 2 decades—by an additional 78 million Americans. Given the high enrollment and likelihood that enrollment will continue to grow, Medicare will continue to be a significant driver of trend.
MEDICARE SPENDING GROWTH

The top five categories of prescription drug spending for Medicare enrollees in 2008 were cardiovascular (29.5%), central nervous system (19.5%), gastroenterology (10.1%), endocrine and diabetes (8.4%), and respiratory (7.5%). Most enrollees in Medicare plans are 65 years of age or older, so their extensive use of drugs in these categories is expected.

A more detailed picture of prescription drug spending under Medicare is presented in Figure 11. The top two therapeutic classes, lipid-lowering and antihypertensive drugs, accounted for almost a quarter of all plan spending in 2008. Treatments for acid-peptic disorders, diabetes, and respiratory conditions also contributed significantly to plan spending.

Plan costs for enrollees of Medicare prescription drug plans (PDPs), based on the standard benefit defined in Medicare Part D as well as Medicare Advantage prescription drug plans (MA-PD) under Medicare Part C, increased by 6.8%. Unit costs for Medicare enrollees increased 4.7% and utilization grew 2.1%. Costs for employer-primary coverage plans increased 6.5%. Unit costs increased 3.2% and utilization increased 3.3%.

1The analysis of Medicare trend is based on 2 years’ data on pharmaceutical spending by enrollees in Medicare Part D (PDP, MA-PD) plans managed by Medco. Plan spending is the net cost to plan sponsors after discounts, rebates, subsidies, and member cost share have been applied. The analysis does not include prescription drug spending under Medicare Part B.

2The analysis of Medicare trend is based on 2 years’ data on pharmaceutical spending by enrollees in commercial (employer-primary) plans managed by Medco. Plan spending is the net cost to plan sponsors after discounts, rebates, subsidies, and member cost share have been applied. The analysis does not include prescription drug spending under Medicare Part B.
MEDICARE TREND DRIVERS

The therapeutic categories with the largest impact on Medicare trend are shown in Figure 12. Plan costs increased most rapidly for selected neurological, cancer and transplant drugs, and respiratory. Plan costs declined sharply for allergy and lipid-lowering drugs.

With the exception of ulcer and heartburn drugs, a substantial portion of Medicare trend was driven by increases in unit costs. Similar to the unit-cost growth for commercial benefit plans as a whole, use of single-source brand-name drugs drove this acceleration.

Utilization growth was driven primarily by three therapeutic classes: selected neurologicals, seizure, and antipsychotics. Utilization growth also accelerated for lipid-lowering drugs (3.5%). However, this growth was offset by the significant reduction in unit costs (-7.5%) associated with the increased use of generics, such as simvastatin.

Demographics of trend

Trends in prescription drug use reflect the interaction of numerous factors. For example, prescription drug use can be affected by patient sociodemographics as well as by regional differences in clinical practice.

AGE-GROUP VARIATIONS

In 2007, drug trend was highest for persons under 49 years of age and lowest for those over age 65 (Figure 13). In contrast, in 2008, drug trend was highest for those under 19 years of age and lowest for those over age 65.

Figure 13. Drug trend by age group in 2008
Source: Medco data

The decline in trend for those over 65 years of age may be due to the fact that a major driver of trend for this age group is the predominant use of generics (e.g., lipid-lowering agents). Although drug trend was lowest for those over age 65, seniors showed the highest rate of spending (Figure 14).
The types of drugs utilized also varied as a function of age because different medical conditions typically dominate different age groups (Figure 15). Drugs used to treat CNS conditions, such as antipsychotics, hypnotics, antianxiety, and ADHD drugs, were frequently utilized by young adults. The low trend for CNS drugs among seniors may be due to recent studies that raised safety concerns about the use of antipsychotics in the elderly and the large number of generic antidepressants now available. In general, the use of cardiovascular and endocrine and diabetes drugs tended to increase with age.

Note: For the top seven categories of spending in 2008, the figure shows the category’s contribution to spending for each age group. Therapeutic categories are rank-ordered from the largest overall contributor to spending at the bottom to the smallest at the top.
**GEOGRAPHIC VARIATIONS**

Prescription drug use varied widely across the United States (Figure 16). In the 10 states with the highest drug utilization rates, risk for inactivity was higher than the national average. Regular exercise has been shown to help delay the onset or aid the management of some chronic conditions, such as high blood pressure, high cholesterol, type 2 diabetes, and osteoporosis. Physical activity also is associated with better weight management and improved mood. Given the protective value of adequate levels of physical fitness, some of the treatment variations observed in different states may be due to regional differences in the level of physical activity.

Figure 16. Drug utilization by state in 2008
Source: Medco data

Note: The states are grouped into five quintiles from highest to lowest utilization. The key shows the range of these average values for the states in each quintile. For the 10 states with the highest utilization, the symbols denote those with above average risks for no physical activity within last 30 days of survey.
National trend

In 2008, the Centers for Medicare & Medicaid Services (CMS) estimated that prescription drugs accounted for 9.9% of national healthcare spending (Figure 17). This percentage is lower than the 10.3% reported in 2007. CMS posits that the deceleration in prescription spending is likely due to the effects of the recession, which may be causing some consumers to shift from more expensive brand-name drugs to cheaper generics and to fill fewer prescriptions.

Healthcare spending growth continues to be driven by the rising costs of hospital care and physician services (Figure 18).
CMS projects that national drug spending will accelerate beginning in 2010 because of anticipated improvements in economic conditions, the effect of new indications for currently approved drugs, and the faster pace of growth among generics (Figure 19). The launch of a large number of first-in-class generics in 2011 and 2012 is expected to moderate the spending growth of this component of healthcare. The spending growth for drugs continued to grow at a slower pace than the growth rate for hospital care (7.2%) and physician and clinical services (6.2%).

Figure 19. National healthcare cost trends from 2004 to 2016
Source: CMS

*CMS projection
THE DYNAMICS OF FUTURE TREND

GENERICS VS. SPECIALTY DRUGS
Looking ahead over the next 3 years, specialty, biotechnology, and orphan drugs will slowly take the lead—but we still expect low to mid single-digit drug cost trend.

- **Key developments that will shape changes in utilization and cost:**
  - A leading driver of future trend will include new and existing specialty and protein-based drugs for common and rare conditions.
  - Therapeutic approaches relying on genomic information and genomic testing in order to personalize therapy will become much more common.
  - Drug price inflation and unit-cost growth will be moderated by the wave of first-time generics for traditional drugs in high cost categories, expected to peak soon after 2011.
  - A pathway for biosimilars could generate a significant new wave of cost savings opportunities as lower-cost versions of some biologics become available. This new wave of biosimilars will rise slowly after 2012 and continue to build to 2020.

- **Adjust your plan to keep pace with projected change.**
  Plan designs and coverage policies should be adjusted to keep pace with future events that are already in view—new traditional and specialty drugs, new biomarker and genomic testing protocols, and new generics and follow-on biologics or biosimilar versions for blockbuster biologics.

**Trend projections**

Over the next few years, drug trend will be shaped by modest increases in treatment rates, high price inflation among traditional and biotech brands that lack generic competition, and cost offsets due to favorable changes in product mix driven by pipeline first-time generics.

Advances in drug development will produce new, higher-cost therapies for cancer; coagulation disorders; central nervous system (CNS) disorders; immune-mediated disorders, such as rheumatoid arthritis (RA), inflammatory bowel disease, psoriasis, and systemic lupus erythematosus (SLE); enzyme-deficiency disorders; and other rare diseases. All this will occur against a backdrop of economic turbulence, increasing use of genomic and protein biomarkers to guide therapy, and efforts to reform healthcare.

This report examines the impact of about 130 drugs in the pipeline and over 30 first-time generics expected to come to market over the next several years. About 49 of the pipeline drugs are likely to fall into the specialty category, and 30 or so will be used to treat rare or “orphan” diseases.

The drugs highlighted in this report will be of significant interest to payers because:

- They may offer effective treatments for diseases that currently lack them.
- Many of the new drugs are expected to be costly and will have been studied only for certain narrow uses or for certain small populations of patients at the time of approval, which creates a need to consider prior authorization strategies.
- Some new drugs in the pipeline will utilize biomarkers or genomic information to identify patients who will or will not benefit or who could be harmed by these agents.
  - These test results could also be used as part of the prior authorization strategy.
- Some new drugs may be more expensive treatments without a clear advantage over existing brands or new generics.
  - Step-therapy protocols may need to be considered in some cases.
This section provides highlights of what lies ahead—pipeline drugs, new indications, new first-time generics, over-the-counter (OTC) switches, biosimilars, personalized approaches to pharmaceutical care—and their collective potential impact on trend. These developments continue to present challenges and opportunities for innovative plan designs and coverage management.

**TREND FORECAST: THE NEXT 3 YEARS**

Medco expects the average ingredient-cost–based drug trend for plan sponsors to increase between 3% and 7% annually over the next 3 years, with the lower single-digit trend toward the beginning of this period (Table 1). These projections are computed at the ingredient-cost level, unadjusted for future changes in discounts, rebates, cost sharing, and Medicare retiree drug subsidies. This year, Medco has based its projections on ingredient costs rather than on Average Wholesale Price (AWP), which was used in the past, because generic dispensing rates are at record levels and AWP may soon be replaced by another cost benchmark. Ingredient-cost trend will more accurately reflect the trend impact from the large number of drug products expected to go generic in the next 3 years.

Table 1. Drug trend projection for 2009–2011*

<table>
<thead>
<tr>
<th>Year</th>
<th>Utilization increase</th>
<th>Price and mix increase</th>
<th>Annual total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>0% to 1%</td>
<td>3% to 5%</td>
<td>3% to 5%</td>
</tr>
<tr>
<td>2010</td>
<td>0% to 1%</td>
<td>4% to 6%</td>
<td>4% to 5%</td>
</tr>
<tr>
<td>2011</td>
<td>1% to 2%</td>
<td>4% to 5%</td>
<td>5% to 7%</td>
</tr>
</tbody>
</table>

*Projected change in drug spending on a plan ingredient cost per-member per-year (PMPY) basis

As in the past, plan sponsors with less aggressive coverage management and plan design strategies are more likely to have a drug trend toward the upper limit of the estimated range. Plan sponsors that aggressively manage the benefit by adjusting coverage policies, expanding incentives for generic utilization, and adjusting member cost share for inflation are likely to experience spending growth toward the lower limit of this range or below.

Unit-cost growth, driven mostly by price inflation among the top single-source brands, is expected to significantly exceed utilization growth as a trend component over the next 3 years. Price inflation among the major brands is expected to account for about 75% of trend during this forecast period. In 2008, brand price inflation averaged about 8% and price inflation among generics was less than 0.5%.

**FORECASTING TRENDS**

Anticipated market developments are combined with 3-year historical utilization and ingredient-cost data to provide forecasts for the following components of drug trend:

- **Utilization**—changes in the number of users and number of days of therapy per user
- **Mix**—changes in unit cost because of shifts in market share from generic to brands and brands to brands in the same category
- **Price**—changes in unit cost because of increases in manufacturers’ prices for existing drugs

The 2009–2011 drug trend forecast is based on utilization and cost data over a 3-year historical period (2006–2008) for a large set of clients with integrated retail and mail-order benefits. The average monthly enrollment in the data sample was over 40 million members. This year’s projections include members enrolled in Medicare Part D plans.
KEY TREND DRIVERS

Trend projections reflect many factors likely to affect future unit costs and utilization, including:
- New specialty and traditional drug approvals
- New or expanded indications for existing drugs
- New dosage forms
- New combination products
- Use of new pharmacogenomic testing approaches
- Patent expirations and first-time generics
- Expected OTC conversions
- Research findings and clinical recommendations likely to affect prescribing practices
- Changes in disease prevalence, disease recognition, or diagnostic and treatment criteria

Over the next 3 years, more than 85% of drug cost trend will be driven by drugs in 6 of the 16 broad chapters in the Preferred Prescriptions® Formulary (Figure 1). The cardiovascular and endocrine/diabetes chapters will account for about 40% of the spending growth. Detailed projections at the ingredient-cost level for the top therapeutic categories begin on page 57.

Within these broader chapters, eight drug classes—including diabetes treatments, anticoagulant/antiplatelet therapies, respiratory disease treatments, antihypertensives, rheumatological drugs, lipid-lowering drugs and drugs for cancer—will account for almost 60% of ingredient-cost spending growth over the next 3 years (Figure 2).

Figure 1. Top therapeutic chapters contributing to projected drug trend (2009–2011)
Source: Medco projection

Figure 2. Top therapeutic classes contributing to projected drug trend (2009–2011)
Source: Medco projection

Note: The figure shows the therapeutic chapters that are likely to drive the majority of spending growth between 2009 and 2011. Data are expressed as a percentage of the total projected increase in plan ingredient cost.
Market projections

- NATIONAL DRUG TREND

The Centers for Medicare & Medicaid Services (CMS) estimates that national healthcare spending grew by 6.1% in 2007. Prescription drug spending grew at the historically low rate of 4.9%—less than the recent low of only 5.8% in 2005 and the slowest rate of drug spending growth since 1963. The healthcare portion of gross domestic product reached 16.2%, up from 16% in 2006. According to CMS, this low growth in prescription drug spending accounted for more than half of the 2007 slowdown in overall national health spending growth, and was attributed to increased generic dispensing, the impact of generics on overall drug price inflation, and growing concern about drug-related safety issues.

CMS predicts that the annual increase in national drug expenditures will average between 6% and 7% per year over the next 10 years. Growth in national drug expenditures will be 3.5% in 2008, 4.5% in 2010, and 6.6% in 2013, and then it is expected to accelerate to 8.6% by 2018. The volume of first-time generic introductions during 2011 to 2012 will help moderate growth in 2012 and 2013. However, new drug introductions and leveling off of first-time generic introductions after 2014 will result in accelerating spending growth from 2014 to 2018.

- DRUG PIPELINE

The world’s top pharmaceutical companies have about 2,000 drugs in clinical development in the top 10 therapeutic categories. Oncology drugs continue to be the largest area of new drug development (Figure 3). Some of these new therapies will involve genetic-based information from patients or tumor biomarkers to determine the appropriateness of a particular therapy for a specific patient.

Approximately 530 of the drugs in clinical development are in Phase III or Phase II/III clinical trials in the United States (U.S.), and about 1025 drugs are in Phase II. About one-third to one-half of the products in Phase III development are new molecular entities (NMEs), new therapeutic biologics, or new vaccines/blood products; the remainder involve new indications for existing drugs, new combination products, new dosage forms, or new routes of administration.

Since passage of the Orphan Drug Act about 25 years ago, over 320 orphan drugs or orphan indications for existing drugs have been approved. Orphan conditions are rare diseases affecting less than 200,000 patients, such as hypereosinophilia, angioedema, and multiple sclerosis (MS). Since 2006, almost one-third of the NME approvals have been for orphan drugs. Because these drugs, which are often costly, are intended for use in underserved patient populations, they may be treated favorably by the Food and Drug Administration (FDA) and ushered quickly through the review process. More than 6,000 rare or orphan diseases affect about 25 million Americans altogether, and many of these diseases will be targets for future drug development.
In 2007, the number of billion-dollar blockbuster drugs fell from 52 to 48 because of the introduction of first-time generics for some major brands. This pattern of fewer blockbusters is expected to continue because many blockbusters are expected to lose patent protection over the next few years. However, potential new blockbuster drugs are expected to come to market in the next few years to take the place of those that have lost blockbuster status. These new blockbusters will include new specialty and nonspecialty medications for cancer, diabetes, immunological diseases, cardiovascular disorders, and neurological diseases.

Some of the possible future blockbusters include prasugrel (an antiplatelet drug for preventing thrombotic events), rivaroxaban (a new oral anticoagulant), denosumab (an injectable biologic for osteoporosis), ustekinumab (a biologic for psoriasis), golimumab (a tumor necrosis factor [TNF] inhibitor for RA), and naproxcinod (a novel nonsteroidal anti-inflammatory drug [NSAID] that releases the chemical nitric oxide).

**New drug approvals**

Across all the drugs in the pipeline, an average of 30 to 35 new drug approvals is possible in each of the next 3 years. In 2008, the FDA increased the rate of new drug approvals. Just 16 NMEs and 7 therapeutic biologics, blood products, or vaccines were approved in 2007. In 2008, the Center for Drug Evaluation and Research (CDER) approved 21 NMEs and 3 biologics, and the Center for Biologic Evaluation and Research (CBER) approved 7 new Biologic License Applications (BLAs) for vaccines and blood products, for a total of 31 new approvals.

In 2008, the FDA also extended the user-fee end dates on more than a half-dozen new drug applications (NDAs), leaving a significant number of pipeline drugs on track for possible approval in the first half of 2009. Many of these approval delays in 2008 seemed attributable to the increased emphasis on Risk Evaluation and Mitigation Strategy (REMS) programs under the Food and Drug Administration Amendment Act (FDAAA) and possible staffing shortages that the Agency is addressing. The Agency seems intent on using its powers under the FDAAA to require more REMS programs. For example, the FDA recently announced that REMS programs would be required for a large number of long-acting narcotic analgesic products.

At the end of January 2009, about 50 new drugs or biologics were already past their user-fee end date or have user-fee goals before the end of 2009. The number of drugs pending FDA approval, combined with those that will be submitted in 2009, could mean a rebound in new drug approvals for 2009, 2010, and 2011.

**New indications**

Expanding the labeled indications for currently approved drugs, especially specialty drugs, continues to be a focus for product development. Gaining a new indication expands the current market or creates a new market for an existing product at lower cost to the manufacturer than developing a new drug.

Some of the new uses being pursued by pharmaceutical manufacturers are shown in Table 2. A number of these new indications, if approved, could have a significant impact on utilization and spending growth over the next several years. For example, approvals for new indications are being sought for Avodart® (prevention of prostate cancer), Cymbalta® (treatment of osteoarthritis and lower back pain), and Pristiq® (fibromyalgia and treatment of postmenopausal symptoms). These new indications could represent significant new user populations for these brand-name drugs, which could contribute to rising utilization.

**New dosage forms and combination products**

New extended-release dosage forms, combination products, and drug-delivery systems continue to be a part of product development and represent a number of pending NDAs. Examples include lamotrigine extended release, gabapentin extended release, naproxen/esomeprazole, choline fenofibrate/rosuvastatin, fluticasone/formoterol, aliskiren/valsartan, and several abuse-resistant narcotic analgesic products. Some of these new products will compete for market share with existing or soon-to-be-released generics. Thus, plans should be prepared to implement coverage management programs as needed.
### Table 2. Some new indications pending FDA approval and in Phase III clinical trials*

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
<th>New indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actos®</td>
<td>pioglitazone</td>
<td>Plaque psoriasis</td>
</tr>
<tr>
<td>Alinia®</td>
<td>nitazoxanide</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td>Amitiza®</td>
<td>lubiprostone</td>
<td>Opioid-induced bowel dysfunction</td>
</tr>
<tr>
<td>Arcalyst®</td>
<td>rilonacept</td>
<td>Prevention of gout flares in patients initiating urate-lowering therapy</td>
</tr>
<tr>
<td>Avastin®</td>
<td>bevacizumab</td>
<td>Pancreatic cancer; renal cell carcinoma, prostate cancer, refractory ovarian cancer, in combination with Tarceva® as second-line for non–small-cell lung cancer</td>
</tr>
<tr>
<td>Avodart®</td>
<td>dutasteride</td>
<td>Reduction in risk for prostate cancer</td>
</tr>
<tr>
<td>CellCept®</td>
<td>mycophenolate</td>
<td>Lupus nephritis, pemphigus vulgaris</td>
</tr>
<tr>
<td>Cialis®</td>
<td>tadalafil</td>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Cinzbia®</td>
<td>certolizumab pegol</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Cymbalta®</td>
<td>duloxetine</td>
<td>Chronic lower back pain, osteoarthritis pain</td>
</tr>
<tr>
<td>Farnest®</td>
<td>toremifene</td>
<td>Reduction in risk for prostate cancer in high-risk patients, treatment of side effects from androgen-deprivation therapy</td>
</tr>
<tr>
<td>Fentora®</td>
<td>fentanyl buccal tablet</td>
<td>Breakthrough pain in patients with chronic non-malignant pain</td>
</tr>
<tr>
<td>HP Acthar® gel</td>
<td>corticotropin gel</td>
<td>Infantile spasms</td>
</tr>
<tr>
<td>Humira®</td>
<td>adalimumab</td>
<td>Ulcerative colitis, asthma</td>
</tr>
<tr>
<td>Kepivance®</td>
<td>palifermin</td>
<td>Mucositis associated with chemotherapy for solid tumors</td>
</tr>
<tr>
<td>Lucentis®</td>
<td>ranibizumab</td>
<td>Diabetic macular edema</td>
</tr>
<tr>
<td>Lyrica®</td>
<td>pregabalin</td>
<td>Postoperative pain</td>
</tr>
<tr>
<td>Nexavar®</td>
<td>sorafenib</td>
<td>Non–small cell lung cancer, malignant melanoma</td>
</tr>
<tr>
<td>Nplate®</td>
<td>romiplostim</td>
<td>Chemotherapy-induced thrombocytopenia</td>
</tr>
<tr>
<td>Nuvigil®</td>
<td>armodafinil</td>
<td>Excessive sleepiness associated with Parkinson’s disease</td>
</tr>
<tr>
<td>Orencia®</td>
<td>abatacept</td>
<td>Systemic lupus erythematosus (subcutaneous dosage form)</td>
</tr>
<tr>
<td>Prestig®</td>
<td>desvenlafaxine</td>
<td>Fibromyalgia, postmenopausal vasomotor symptoms</td>
</tr>
<tr>
<td>Relistor®</td>
<td>methylprednisolone</td>
<td>Opioid-induced constipation in patients with chronic pain</td>
</tr>
<tr>
<td>Revlimid®</td>
<td>lenalidomide</td>
<td>First-line for multiple myeloma, chronic lymphocytic leukemia, non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Rituxan®</td>
<td>rituximab</td>
<td>Relapsing-remitting multiple sclerosis, systemic lupus erythematosus</td>
</tr>
<tr>
<td>Sutent®</td>
<td>sunitinib malate</td>
<td>Breast, lung, colorectal cancer</td>
</tr>
<tr>
<td>Tarceva®</td>
<td>erlotinib</td>
<td>First-line for non–small cell lung cancer, colorectal cancer</td>
</tr>
<tr>
<td>Tekturna®</td>
<td>aliskiren</td>
<td>Combination use with an ACE inhibitor for prevention of diabetic nephropathy</td>
</tr>
<tr>
<td>Torisel®</td>
<td>temsirolimus</td>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>Tracleer®</td>
<td>bosentan</td>
<td>Combination use with sildenafil for pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Tykerb®</td>
<td>lapatinib</td>
<td>Head and neck cancer, first-line for breast cancer</td>
</tr>
<tr>
<td>Ventavis®</td>
<td>iloprost</td>
<td>Combination use with sildenafil for pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Xifaxan®</td>
<td>rifaximin</td>
<td>Hepatic encephalopathy, diarrhea-associated irritable bowel syndrome</td>
</tr>
<tr>
<td>Xyrem®</td>
<td>sodium oxybate</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>Zyflo CR®</td>
<td>zileuton</td>
<td>Chronic obstructive pulmonary disease in adults</td>
</tr>
</tbody>
</table>

* Will likely be a specialty drug for this indication.

**FIRST-TIME GENERICS**

Drugs with total 2008 U.S. sales of nearly $34 billion could lose patent protection over the next 3 years, expanding the market for lower-cost generics (Table 3). The next 3-year period of first-time generics will represent slightly more than half of the total of about $66 billion in current drug spending that could be affected by generic competition over the next 5 years. This pool of first-time generics represents a significant opportunity for savings and a means to help offset costs associated with new drug introductions over this time.

Many of the anticipated first-time generics over the next 3 years are shown in Table 3. The number of first-time generics could be even greater if generic manufacturers continue to launch new generics on an at-risk basis (before patent disputes are settled) or secure favorable outcomes in ongoing patent litigation. An approval pathway for biosimilars does not yet exist, so this table does not list biologics with expired patents or those that could lose patent protection in the next 3 years.
### Table 3. Some potential patent expirations for 2009–2011

<table>
<thead>
<tr>
<th>Possible patent expiration</th>
<th>Brand name (generic name), manufacturer</th>
<th>Use</th>
<th>2008 U.S. retail sales ($M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Ambien CR® (zolpidem controlled-release), Sanofi-Aventis</td>
<td>Insomnia</td>
<td>$986</td>
</tr>
<tr>
<td></td>
<td>Topamax® (topiramate), Ortho-McNeil</td>
<td>Seizure disorders, migraine headache</td>
<td>$2,356</td>
</tr>
<tr>
<td></td>
<td>Casodex® (bicalutamide), AstraZeneca</td>
<td>Prostate cancer</td>
<td>$228</td>
</tr>
<tr>
<td></td>
<td>Prandin® (repaglinide), Novo Nordisk</td>
<td>Type 2 diabetes</td>
<td>$153</td>
</tr>
<tr>
<td></td>
<td>Fosamax Plus D™ (alendronate/cholecalciferol), Merck</td>
<td>Osteoporosis</td>
<td>$240</td>
</tr>
<tr>
<td></td>
<td>CellCept® (mycophenolate mofetil), Roche</td>
<td>Transplant rejection</td>
<td>$777</td>
</tr>
<tr>
<td></td>
<td>Prevacid® (lansoprazole), Novartis</td>
<td>Ulcers, gastroesophageal reflux disease</td>
<td>$2,948</td>
</tr>
<tr>
<td></td>
<td>Clarinex® (desloratadine), Schering</td>
<td>Allergies</td>
<td>$251</td>
</tr>
<tr>
<td></td>
<td>Adderall XR® (amphetamines salts), Shire</td>
<td>Attention deficit hyperactivity disorder</td>
<td>$1,585</td>
</tr>
<tr>
<td></td>
<td>Pulmicort Respules® (budesonide), AstraZeneca</td>
<td>Asthma</td>
<td>$876</td>
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<tr>
<td></td>
<td>Voltrex® (valacyclovir), GlaxoSmithKline</td>
<td>Viral infections</td>
<td>$2,020</td>
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<tr>
<td></td>
<td>Cozaar® (losartan), Merck</td>
<td>Fecha:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyzaar® (losartan/hydrochlorothiazide), Merck</td>
<td>Fecha:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flomax® (tamsulosin), Boehringer Ingelheim</td>
<td>Fecha:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Effexor XR® (venlafaxine extended-release), Wyeth</td>
<td>Fecha:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arimidex® (anastrozole), AstraZeneca</td>
<td>Breast cancer</td>
<td>$657</td>
</tr>
<tr>
<td></td>
<td>Rapamune® (sirolimus), Wyeth</td>
<td>Transplant rejection</td>
<td>$136</td>
</tr>
<tr>
<td></td>
<td>Differin® (adapalene topical), Galderma</td>
<td>Acne</td>
<td>$282</td>
</tr>
<tr>
<td>2011</td>
<td>Xalatan® (latanoprost ophthalmic solution), Pfizer</td>
<td>Glaucoma, ocular hypertension</td>
<td>$494</td>
</tr>
<tr>
<td></td>
<td>Acolate® (zafirlukast), AstraZeneca</td>
<td>Asthma</td>
<td>$44</td>
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<tr>
<td></td>
<td>Aricept® (donepezil), Eisai</td>
<td>Alzheimer’s disease</td>
<td>$1,224</td>
</tr>
<tr>
<td></td>
<td>Levaquin® (levofloxacin), Ortho-McNeil</td>
<td>Bacterial infections</td>
<td>$1,719</td>
</tr>
<tr>
<td></td>
<td>Patanol® (olopatadine ophthalmic solution), Alcon</td>
<td>Allergic conjunctivitis</td>
<td>$256</td>
</tr>
<tr>
<td></td>
<td>Actos® (pioglitazone), Takeda</td>
<td>Type 2 diabetes</td>
<td>$2,569</td>
</tr>
<tr>
<td></td>
<td>Temodar® (temozolomide), Schering</td>
<td>Brain cancer</td>
<td>$224</td>
</tr>
<tr>
<td></td>
<td>Zyprexa® (olanzapine), Lilly</td>
<td>Schizophrenia, bipolar disorder</td>
<td>$1,853</td>
</tr>
<tr>
<td></td>
<td>Caduet® (amlodipine/atorvastatin), Pfizer</td>
<td>High blood pressure and high cholesterol</td>
<td>$418</td>
</tr>
<tr>
<td></td>
<td>Lipitor® (atorvastatin), Pfizer</td>
<td>High cholesterol</td>
<td>$6,392</td>
</tr>
<tr>
<td></td>
<td>Tazorac® (tazarotene topical), Allergan</td>
<td>Acne</td>
<td>$109</td>
</tr>
</tbody>
</table>

*Availability dates for first-time generics are subject to significant change as a result of multiple patent protections, patent litigation, pediatric or other exclusivities, at-risk launches, and delays between patent expiration and launch of first-time generics.

*Possible patent expiration assumes a pediatric extension.

*Sales figure includes only the capsule formulation, not the solutabs or powder packets.
The launch of many new, high-volume generics over the next 3 years will help drive down unit-cost growth in several therapeutic categories as utilization shifts to low-cost generic options. Plans need to carefully consider the opportunities for formulary, interchange, and step-therapy protocols as a result of these new generics. Plans also need to consider that as new first-time generics become available, new brands are also being introduced that could counter some of the savings that would otherwise have been realized. For example, the savings from new generics for Fosamax® (alendronate) in 2008 could be countered by the approval of the specialty drug denosumab in 2010. Similarly, the potential savings from first-time generics for Prevacid® could be compromised by introduction of dexlansoprazole (Kapidex™).

PERSONALIZED MEDICINE

Personalized medicine, or pharmacogenomics, involves drug therapy tailored to the specific characteristics of an individual patient.11 Deoxyribonucleic acid (DNA)-based and other diagnostic tests provide the type of individualized information that enables this personalized approach. Integration of genomic technology into day-to-day healthcare will take years to fully achieve, but events during the next few years are likely to shape the evolution of personalized medicine.

Technology trends
Genomic sequencing technology has evolved rapidly since the first human genome sequence was completed in 2003. In fact, what once cost $3 billion and took several years to complete now costs less than $1 million and can be accomplished in less than 2 months.12 During 2008, several molecular testing companies offered partial-genome sequencing services for $1,000 or less.9 Eventually, whole-genome sequencing is likely to be only marginally more expensive than single-gene analysis. Full-genome sequencing will provide a wealth of individualized data that can be accessed later to inform clinical decision making. However, one of the primary challenges will be linking the wealth of information on various genotypes to discernible levels of risk for development of a disease or condition.

Policy trends
Congress enacted the Genetic Information Non-discrimination Act (GINA) in mid 2008 to protect the privacy of patients who undergo genetic-based diagnostic testing. This act may partially assuage concerns about misuse of genetic information, a perceived barrier to more broad-scale use of genetic testing.

Value for money spent, and who will pay for genomic testing, are the subject of strong debate, and the anticoagulant drug warfarin is at the center of this debate. Genetic testing can determine a person’s intrinsic sensitivity to the blood-thinning effects of warfarin (VKORC1), as well as an individual’s ability to metabolize the drug (CYP450-2C9). Both parameters influence the dose of warfarin needed to adequately prevent clot formation and minimize bleeding events. Some view genomic testing as a potential means for reducing warfarin-related toxicity (bleeding, hospitalization); others believe that more data may be needed before any value determination can be made. CMS is currently evaluating the warfarin genomic tests and plans to issue a coverage recommendation by mid 2009. This CMS policy will likely determine if the test will be covered under the federal plans, and will also influence the opinions of many payers regarding coverage/reimbursement of the test. The outcome of Medco’s own ongoing study of warfarin is expected in late 2009 and should help further characterize the value of the warfarin genetic testing.

Treatment trends
During the next few years, the greatest impact on treatment practices is likely to come from identification of biomarkers relating to existing and near-term pipeline drugs, particularly those with questionable efficacy, high toxicity, or considerable dosing variability. This treatment trend is already reflected in the recent American Society of Clinical Oncology Provision Clinical Opinion (PCO) that all patients with metastatic colon cancer who are candidates for anti-epidermal growth factor receptor (anti-EGFR) therapy have their tumors tested for KRAS gene mutations. If a tumor has a mutated KRAS gene, then an anti-EGFR antibody, such as Erbitux® or Vectibix®, should not be used. This recommendation could save plan sponsors and patients hundreds of millions of dollars annually in the cost of Erbitux alone and help improve treatment outcomes.13
A recent analysis found that the package inserts of approximately 25% of prescription drugs contain genomic information, but not all this information can be used to make treatment decisions. The following examples highlight how pharmacogenomics testing can influence drug function or metabolism:

- **Selzentry®** is a novel antiviral drug indicated for treating HIV in patients infected with a specific strain of virus that targets the CCR5 protein to gain cellular entry. This viral behavior (tropism) can be evaluated using a specific diagnostic test.
- **Tamoxifen** is an anticancer agent that requires activation via liver enzymes (CYP450-2D6) in order to generate the active form, endoxifen. The function of this liver enzyme is variable and testing can identify patients who are considered “poor metabolizers” for whom alternative therapy may be considered.
- **Tegretol®** may cause severe skin reactions in patients who carry the human leukocyte antigen B (HLA-B)*1502 allele. Testing may identify carriers of this biomarker, allowing an alternative anticonvulsant to be prescribed.
- **Xenazine®** (tetrabenazine) is a novel treatment for Huntington's disease. Because of side effects, the drug requires careful dosing. The prescribing information recommends genotyping for liver enzyme function (CYP450-2D6) for patients who require doses greater than 50 mg per day.

**Pipeline companion diagnostics and drugs**

Several drugs in the pipeline are being codeveloped with molecular diagnostic tests (also called “companion diagnostics”) that help identify the target treatment population. Examples include:

- The atypical antipsychotic iloperidone may be approved with a companion diagnostic that identifies patients with schizophrenia who are more likely to respond to the drug. Iloperidone was denied FDA approval in 2008 but was resubmitted later in that year and may reach the market in 2009.
- **Bucindolol** (Gencaro™) is a new cardiovascular beta-/alpha-blocker that may be approved in 2009 for congestive heart failure. A test has been developed that identifies the genotype of the beta and alpha receptors, which correlate with positive treatment outcomes. Gencaro could be marketed in mid 2009.
- **Vilazodone** is an antidepressant that is being codeveloped with a diagnostic test that identifies patients who are more likely to respond to vilazodone therapy. The identity of the biomarker is not yet known, but the same company is developing both the drug and the companion diagnostic test, which are expected to reach the market in 2011.

It is unclear how much the use of a companion diagnostic strategy will improve the long-term market success of a drug. However, several pipeline drugs, especially in oncology, are linked to drug-response biomarkers. The wave of personalized medicine is just beginning to build, and the future will bring many new approaches that should lead to overall improvement in healthcare. Plan designs should address this wave of pharmacogenomics testing by providing coverage for companion diagnostics and various genetic tests used to identify patients who will or will not respond, or who might respond differently than expected, to a drug.

**BIOSIMILARS (FOLLOW-ON BIOLOGICS)**

Protein-based drugs, most of which are produced using recombinant DNA technologies, are playing an increasingly important role in the treatment of many conditions. In fact, since the first recombinant human insulin product entered the market in 1982, over 100 different recombinant protein-based drugs have been approved. Another 400 biologics and protein-based drugs are in various stages of clinical development. Biologic or protein-based drug therapies account for about 16% of prescription-drug spending, and the drug trend for biologics is growing at a much faster rate than that for non–protein-based drugs. The lack of availability of lower-cost competitors is one of the factors contributing to the rapid growth in spending for these drugs.

**A pathway for generics**

A major barrier to the market availability of biosimilars is the lack of a regulatory pathway. Most protein-based drugs or biologics on the market today were originally approved under the Public Health Services Act (PHSA) of 1944, which does not contain provisions for approval of generic versions. Several regulatory approaches that would have permitted applications for licensure of biosimilars were proposed in 2007 and 2008. Some of these proposals allowed for FDA determination of interchangeability with a reference product and others did not. These proposals have also included
periods of market exclusivity for the original biologic product and for the first approved biosimilar versions of the reference product. These periods of exclusivity have varied from 5 to 14.5 years for the reference product. Traditional drugs receive 5 years of exclusivity under the Hatch-Waxman amendment, and orphan drugs receive 7 years of exclusivity under the Orphan Drug Act. In Europe where the approval pathway has already been defined, biosimilars are granted 10 years of exclusivity. Unlike patents, exclusivity cannot be invalidated because there is little legal means to overcome a period of exclusivity. Also, unlike the case with traditional drugs, with biologics the patents on the manufacturing processes are relevant and must be overcome or expire before a biosimilar product can be launched.

**What to expect in the future**

Creation of a pathway to market for biosimilars appears to be only a year or two away in the United States, and the first biosimilar could come to market within a year or two after that. In March 2009, the Promoting Innovation and Access to Life-Saving Medicine Act was introduced by Henry Waxman (D-California) and others; thus, the 2009 legislative year has already seen the introduction of at least one bill to move the pathway forward.

Estimates of the potential savings from biosimilars have ranged from $10 billion to hundreds of billions of dollars. Differences among these estimates reflect such factors as differing assumptions about future patent expirations, periods of exclusivity, pricing strategies for the brand and follow-on versions, and development of new analytic technology to determine comparability. The introduction of biosimilars will probably start in 2012, and savings from these products will build slowly over many years.

Recent announcements that some major pharmaceutical manufacturers plan to develop biosimilars suggest that competition may be vigorous in the space. Large pharmaceutical companies have all the necessary experience and ability to succeed in this area, including marketing, clinical trials, and manufacturing experience. A few larger generic manufacturers and small biotech companies also intend to compete. Even so, only two or three biosimilars are expected to compete with any reference-brand biologic. Also, competitors may be more interested in products with larger user populations and sales, so price discounts are expected to be smaller than those for traditional generics.

One way for plans to position themselves to take advantage of the coming wave of biosimilars is to create a lower co-payment tier for biosimilars than for the originator biologic brand. This design should likely be put in place before biosimilars hit the market.

- **RX-TO-OTC SWITCHES**

The conversion of prescription drugs to OTC status is a continuing trend. OTC versions of Zyrtec® (cetirizine) came to market in 2008. OTC conversion of another non-sedating antihistamine, Clarinex® (desloratadine), is expected in 2009. Novartis has acquired the rights to market OTC versions of Prevacid® (lansoprazole) and is expected to launch an OTC version when the brand patent expires in late 2009. As with Prilosec OTC®, the OTC conversion for Prevacid may be only a partial conversion, with different strengths or formulations available in prescription and OTC form. An OTC version of Zegerid® (omeprazole), which was pushed back in early 2009, could still come to market in the near future.

- **KEY THERAPEUTIC DEVELOPMENTS**

Oncology drugs are again one of the top eight categories that will drive spending growth over the next 3 years (Figure 1). However, drugs for diabetes, anticoagulant and antiplatelet therapies, respiratory drugs, all antihypertensives combined, and rheumatological agents represent the main trend-driving categories for the next 3 years. Since the launch of generics for Zocor® in 2006, cholesterol-lowering drugs have retreated into the background as a trend driver. This therapeutic category will further decrease as a trend driver with the availability of generics for Lipitor® in late 2011.

Specialty, biologic, and orphan drugs will become increasingly important trend drivers over the next 3 years. As more and more patents expire on blockbuster small-molecule drugs, future blockbusters will come from products within the biologics category. Thus, a pathway for approval of biosimilars will become more and more important with time.

Detailed forecasts of developments in these different therapeutic areas are provided in the following sections of this report.
**Cardiovascular agents**

Contribution to plan spending (2008): 22%
Projected contribution to trend (2009 to 2011): 22%

**Projected trend**

Table 4. Drug trend projection for cardiovascular agents*

<table>
<thead>
<tr>
<th>Year</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Utilization increase</td>
<td>Price and mix increase</td>
<td>Annual total</td>
</tr>
<tr>
<td>2009</td>
<td>0% to 1%</td>
<td>2% to 3%</td>
<td>2% to 3%</td>
</tr>
<tr>
<td>2010</td>
<td>2% to 3%</td>
<td>5% to 6%</td>
<td>5% to 6%</td>
</tr>
<tr>
<td>2011</td>
<td>2% to 4%</td>
<td>7% to 9%</td>
<td>7% to 9%</td>
</tr>
</tbody>
</table>

*Projected change in drug spending on a plan ingredient cost PMPY basis

**TREND PREDICTIONS**

**Key developments that are likely to shape drug trend in the cardiovascular category over the next 3 years:**

- Increased use of single-entity and combination drugs that lower cholesterol or lower low-density lipoprotein (LDL) and raise high-density lipoprotein (HDL) cholesterol when used for primary and secondary prevention
- Increased use of more aggressive treatment to achieve lower cholesterol levels
- Broader populations that become candidates for cholesterol-lowering treatment
- Two or more new anticoagulant drugs that could eventually replace warfarin
- New antiplatelet drugs used alone or in combination with standard therapy for treating and preventing arterial thrombotic events and reducing the risk of heart attack and stroke
- Unit-cost savings resulting from generic availability in the beta-blocker, statin, angiotensin-converting enzyme (ACE) inhibitor, and calcium channel blocker categories
- First-time generics in the angiotensin II receptor blocker (ARB) category

**Trend drivers:** New antiplatelet and anticoagulant drugs, ARBs, branded statins

**Trend moderator:** Increased use of generic drugs to treat hypertension and high cholesterol

Although significant progress has been made in managing cardiovascular disease (CVD), as evidenced by the 33% decline in age-adjusted CVD in the U.S. population between 1990 and 2004, CVD remains a leading cause of death and disability in the United States. The latest estimates also indicate that one-third of adults are obese and nearly two-thirds are overweight. Excess body weight and obesity place people at risk for diabetes, heart disease, stroke, gallbladder disease, osteoarthritis, and respiratory disease. This epidemic of obesity is also likely linked to the five-fold increase in triglyceride levels seen during the past 3 decades. About one-third of adults now have hypertriglyceridemia. Elevated triglyceride levels are also a risk factor for CHD.
LIPID-LOWERING AND HDL-RAISING DRUGS

Plan ingredient-cost spending on cholesterol-lowering drugs is expected to grow at about 3% to 5% annually over the next 3 years despite continuing reliance on use of generic statins. Generic availability in the category will continue to help moderate unit costs, but rising utilization will counter some of the savings from generics.

New treatment guidelines and study findings

Results from the 1999 to 2004 National Health and Nutritional Examination Survey (NHANES) indicate that about 14 million older adults are currently taking statins and another 18 million are candidates for statin therapy based on current guidelines. The update to the national cholesterol treatment guidelines, Adult Treatment Panel IV, should be available for public comment late in 2009. Use of cholesterol-lowering therapies over the next few years will be driven by these guidelines. In the meantime, the American Diabetes Association (ADA) recommends that statins be considered for all patients with type 2 diabetes over age 40 and for younger patients with risk factors. For patients with type 1 diabetes, statin use should be considered even for children as young as age 10. The American Heart Association (AHA) has also issued guidelines for the use of statins by children aged 10 and older who meet certain high-risk criteria. A recent analysis of LDL and cholesterol levels in children and adolescents in the United States suggests that about 200,000 children might qualify under this guideline for statin therapy. Therefore, the AHA recommendation in children should not have a major impact on utilization of these drugs.

In November 2008, the JUPITER study was published. In this trial, patients without high cholesterol but with elevated C-reactive protein levels received Crestor® or placebo. C-reactive protein is a marker for vascular inflammation and atherosclerotic plaque. In this study, Crestor significantly reduced the incidence of major cardiovascular events compared with placebo. If these results are incorporated into cholesterol treatment guidelines, eventually another 11 million patients could be added to the ranks of statin-eligible patients.

During 2008, Vytarin® suffered a significant setback as a result of the ENHANCE and SEAS trials, in which Vytarin failed to reduce atherosclerotic plaque more than simvastatin alone and failed to improve outcomes in patients with aortic stenosis, respectively. Also, an increased risk of cancer was associated with Vytarin use in the SEAS trial. However, data from other ongoing studies failed to confirm this risk. Proof that this combination improves cardiovascular outcomes will need to await the results from the IMPROVE-IT trial, expected after 2011.

Treatment of low HDL cholesterol

Excessively high serum cholesterol values (240 mg/dL or higher) still affect 16% of adults aged 20 or older and about 19% of adults aged 40 to 59. Furthermore, several million American men and women have too-low HDL values, a significant risk factor for serious cardiovascular events. The next crop of cholesterol management therapies is aimed at lowering LDL levels while simultaneously increasing HDL levels.

Clinical trials for torcetrapib, the first potential entrant in a new class of drugs known as cholesteryl ester transfer protein (CETP) inhibitors, were halted in December 2006 when increased mortality was noted in the active treatment group of a Phase III trial. Most experts have attributed this finding to “off-target” effects of torcetrapib, possibly involving aldosterone-like effects. Research into this novel class of drugs has not been halted, and two other CETP inhibitors, anacetrapib and dalcetrapib, are in Phase III trials and may receive FDA approval, but not until after 2011.

In April 2008, the FDA issued a nonapprovable letter for the combination product laropiprant/niacin extended release. Laropiprant is a prostaglandin D receptor antagonist that reduces the flushing caused by niacin. Whether laropiprant will reduce niacin-induced flushing significantly more than aspirin or will reduce long-term therapy discontinuations significantly more than niacin extended release alone remains to be determined. The FDA has indicated that it will need to await the results of HPS-THRIVE, a long-term outcome study of laropiprant/niacin extended release, before deciding on approval of this new combination. Since these results may not be available until 2011, the introduction of this combination product will likely be delayed.
The National Heart, Lung and Blood Institute is currently conducting a long-term outcome study (AIM-HIGH) to determine whether raising HDL cholesterol with drug therapy confers cardiovascular benefits. This multicenter, randomized trial is designed to assess whether the combination of niacin plus simvastatin is superior to simvastatin alone in delaying time to first major cardiovascular event over a 4-year follow-up period in patients with mixed atherogenic dyslipidemia. Results of this study, expected in 2010 or 2011, will affect the success of any niacin combination product that lowers LDL and also raises HDL levels simultaneously.

Other new cholesterol-lowering drugs
In addition to new CETP inhibitors, a few novel cholesterol-lowering drugs are in the pipeline. For example, mipomersen, a novel antisense compound directed against apolipoprotein B, has been shown to cause incremental reductions in LDL cholesterol and triglycerides when used along with a statin. Antisense drugs target and inactivate messenger RNA, thereby effectively suppressing the activity of a gene that is producing a detrimental clinical effect. This subcutaneously administered drug could be approved by 2011 for use in patients with very high cholesterol levels because of homozygous familial hypercholesterolemia. Additional indications for much larger populations of patients could come after 2011.

A second novel drug that specifically targets atherosclerotic plaque formation—darapladib—is just entering Phase III trials. Darapladib is an orally active inhibitor of lipoprotein-associated phospholipase A2 (Lp-LPA-2), an enzyme linked to atherosclerotic plaque formation.

Impact of new generics
First-time generics for both Zocor (simvastatin) and Pravachol® (pravastatin) were introduced in 2006. By the end of 2008, three generic statins—lovastatin, pravastatin, and simvastatin—accounted for about one-half of the prescription market among the pure statin drugs. These new generics will continue to moderate unit-cost growth as the product mix shifts toward lower-cost options over the next few years. Toward the end of 2011, the mega-blockbuster Lipitor is also expected to lose patent protection. The availability of generics for this high-potency statin will dramatically shift this group of drugs into a largely generic category.

ANTIHYPERTENSIVE DRUGS

Treatment rates
Antihypertensives represent the largest single contributor to utilization within the cardiovascular category, which as a whole is expected to represent about 7% of total drug trend during the next 3 years. From 2001 to 2004, among adults aged 45 to 54, the prevalence of hypertension was 35% for men and 36% for women. For adults older than 75 years, the prevalence was 67% for men and 82% for women. Despite high treatment rates, hypertension is controlled to target goals in only one-third to one-half of patients.

Treatment options
Recent clinical studies indicate that patients who have CHD but not hypertension experience fewer cardiovascular events when taking certain antihypertensive drugs, such as ARBs and ACE inhibitors. However, most of the available evidence suggests that ARBs and ACE inhibitors in combination provide little incremental benefit but may lead to more adverse events. Utilization of the ARB class is likely to continue to increase because these drugs are generally better tolerated than ACE inhibitors and are being employed more widely in patients who have had a heart attack, kidney disease, or heart failure.

Renin inhibitors
The first of a new generation of antihypertensive agents, Tekturna® (aliskiren), came to market in March 2007. However, by the end of 2008, this drug had gained only about a 2% market share in the combined category of ARBs and renin inhibitors. No other renin inhibitors appear to be in the near-term pipeline.
Combination therapy with Tekturna and an ACE inhibitor or an ARB is being investigated for use in diabetic nephropathy. Tekturna plus an ARB appears to reduce blood pressure more than either drug alone. However, other combinations using drugs with different mechanisms are likely to produce greater reductions in blood pressure. Large outcome studies are underway to explore the potential benefits of aliskiren after heart attack and for primary and secondary prevention of CVD.

First-time generics
During 2007, first-time generics became available for a number of cardiovascular drugs, including Norvasc® (amlodipine), Toprol-XL® (metoprolol sustained release), and Coreg® (carvedilol). These new generics created a significant opportunity to reduce unit costs in the antihypertensive category. Unfortunately, in 2009 Toprol-XL returned to single-source status as a result of FDA actions affecting the generic manufacturers in the marketplace.

First-time generic availability in the ARB class should occur when Cozaar® and Hyzaar® go generic in early 2010. These generics will create significant cost-saving opportunities for plans that are positioned to take advantage of them. Generics for other drugs in the ARB class should follow in 2012.

Anticoagulant and antiplatelet drugs

Treatment rates
The use of antiplatelet drugs to prevent heart attack, stroke, and other vascular events continues to grow rapidly. Introduction of new antiplatelet agents and novel oral anticoagulants that do not require intensive coagulation monitoring could add tremendously to growth in this category over the next few years.

Marketplace dynamics
Plavix®, the second largest-selling drug in the world, had its patent upheld in 2007, and generics for this drug should not enter the marketplace again until 2011 or 2012. The focus has now shifted to new antiplatelet drugs that will serve as replacements for or improvements on Plavix.

New drugs
Prasugrel and ticagrelor, new pipeline antiplatelet drugs that are similar to Plavix, are being studied in a variety of settings. Both of these drugs are likely to be introduced before the patent for Plavix expires. In a major study comparing prasugrel and clopidogrel in patients with acute coronary syndrome (ACS) and scheduled percutaneous coronary intervention, prasugrel therapy was associated with significantly fewer ischemic events, including stent thrombosis, than clopidogrel therapy. However, a small increased risk of bleeding, including fatal bleeding, was reported with prasugrel. After several approval delays, an FDA Advisory Committee unanimously recommended approval of prasugrel.

The promise of prasugrel is related to its less variable antiplatelet activity. Recently, several studies have linked genetic mutations in the Plavix metabolizing enzymes to reduced efficacy and a higher rate of cardiovascular adverse events. Unlike Plavix, the efficacy of prasugrel does not appear to be significantly affected by genetic polymorphisms in drug metabolizing enzyme or drug-drug interactions involving inhibition of these same metabolizing enzymes.

A new antiplatelet agent, SCH 530348, with a unique mechanism of action—thrombin receptor inhibition—could also come to market by 2011. This drug targets the thrombin receptor on platelets, and preliminary evidence shows it further reduces vascular risk without any increase in bleeding risk. Since this drug will likely be an add-on therapy, it could increase cost and utilization in the antiplatelet category starting about 2011.

Several novel oral anticoagulants are also in the near-term pipeline. These include rivaroxaban and apixaban, both oral Factor Xa inhibitors, and dabigatran, a reversible direct thrombin inhibitor. Rivaroxaban, which could be approved during the first half of 2009, has shown good efficacy with little compromise in safety in several Phase III studies comparing it with the current standard, Lovenox® (an injectable). FDA approval of dabigatran is also possible by 2010. Although apixaban failed to meet a primary endpoint in a recent Phase III trial, approval by sometime in 2011 is still possible. None of these new oral anticoagulants will require the type of intensive monitoring that warfarin (Coumadin®) requires, possibly giving them a significant advantage. These drugs could also eventually win approval for treatment of deep vein thrombosis and
pulmonary embolism, prevention of stroke in patients with atrial fibrillation, and treatment of ACS. When approved, these agents could become the standard of care for their labeled indications, significantly increasing both utilization and unit cost in the oral anticoagulant drug category.

- **ANTIARRHYTHMICS**

Dronedarone, a new Class III antiarrhythmic drug that is chemically similar to amiodarone, could be approved in 2009. Amiodarone is by far the most frequently used orally administered antiarrhythmic agent.

In the ATHENA trial, which enrolled patients with atrial fibrillation, dronedarone recipients spent 35% fewer days in the hospital for cardiovascular reasons and showed a 24% reduced risk of cardiovascular hospitalization or death over a 2-year period compared to placebo recipients.\(^4^0\) Also, in the DIONYSOS study, dronedarone was associated with a much lower rate of adverse events than amiodarone. Unfortunately, the use of dronedarone was also associated with a higher rate of recurrence of atrial fibrillation and discontinuations for lack of efficacy compared to amiodarone.\(^4^1\) Therefore, this drug may become a second-line option for patients who cannot tolerate amiodarone or perhaps a first-line choice with amiodarone reserved for dronedarone treatment failures.

The availability of a new branded antiarrhythmic agent will increase unit costs in this category of drugs, which has not seen a new entrant in several years. Examples of ambulatory-use cardiovascular drugs in the pipeline are listed in Table 5.

Table 5. Some ambulatory-use cardiovascular agents in the pipeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Generic name</th>
<th>Uses</th>
<th>Potential impact on drug trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>prasugrel</td>
<td>Prevention of stroke and myocardial infarction (MI) in patients after percutaneous coronary intervention</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>dabigatran</td>
<td>Prevention and treatment of deep-vein thrombosis, pulmonary embolism</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td>rivaroxaban</td>
<td>Prevention and treatment of deep-vein thrombosis, pulmonary embolism</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td>dronedarone</td>
<td>Ventricular arrhythmias</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td>bucindolol</td>
<td>Heart failure</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>pitavastatin</td>
<td>High cholesterol</td>
<td>$</td>
</tr>
<tr>
<td>2010</td>
<td>choline fenofibrate + rosvastatin</td>
<td>Hypercholesterolemia/lipid disorders</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>aliskiren + amlodipine</td>
<td>Hypertension</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>aliskiren + valsartan</td>
<td>Hypertension</td>
<td>$</td>
</tr>
<tr>
<td>2011</td>
<td>apixaban</td>
<td>Prevention and treatment of deep-vein thrombosis, pulmonary embolism</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>mipomersen</td>
<td>High cholesterol</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>SCH 530348 (TRA)</td>
<td>Secondary prevention of stroke, myocardial infarction</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td>ticagrelor</td>
<td>Secondary prevention of stroke, myocardial infarction</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>anacetrapib</td>
<td>High cholesterol/low high-density lipoprotein level</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td>darusentan</td>
<td>Refractory high blood pressure</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>darapladib</td>
<td>Reduction of atherosclerotic plaque</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>otamixaban</td>
<td>Acute coronary syndrome</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>choline fenofibrate + atorvastatin</td>
<td>Hypercholesterolemia/lipid disorders</td>
<td>$</td>
</tr>
</tbody>
</table>

$\$$ = potential to cause a 25% increase in this category’s trend.

$ = potential impact <2% increase in this category’s trend.
Central nervous system (CNS) agents

Contribution to plan spending (2008): 22%
Projected contribution to trend (2009 to 2011): 14%

Projected trend

Table 6. Drug trend projection for CNS agents*

<table>
<thead>
<tr>
<th>Year</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utilization increase</td>
<td>1% to 2%</td>
<td>1% to 2%</td>
<td>1% to 2%</td>
</tr>
<tr>
<td>Price and mix increase</td>
<td>2% to 3%</td>
<td>2% to 3%</td>
<td>3% to 4%</td>
</tr>
<tr>
<td>Annual total</td>
<td>3% to 5%</td>
<td>3% to 5%</td>
<td>4% to 6%</td>
</tr>
</tbody>
</table>

*TProjected change in drug spending on a plan ingredient cost PMPY basis

TREND PREDICTIONS

Key developments that are likely to shape drug trend in the CNS category over the next 3 years:
- Continued growth in utilization of antiseizure and antipsychotic medications
- New drugs for the treatment of MS, epilepsy, schizophrenia, depression, and migraine
- New pain medications and reformulations of narcotic pain relievers to discourage abuse
- Increased use of new and existing drugs for fibromyalgia, a pain syndrome
- First-time generics for Imitrex® (sumatriptan), a commonly used antimigraine agent; Topamax® (topiramate), a commonly used antiseizure agent; Adderall XR® (amphetamine salts), a stimulant commonly used for attention deficit hyperactivity disorder (ADHD); Effexor XR® (venlafaxine extended release), an antidepressant; and Aricept® (donepezil), an agent for Alzheimer’s dementia

Trend drivers: Narcotic pain relievers, atypical antipsychotics, branded antidepressants, MS agents
Trend moderators: NSAIDs, selective serotonin reuptake inhibitors (SSRIs), antiseizure medications, sleep agents

SEIZURE DRUGS

Broader indications
Utilization of antiseizure drugs continues to grow briskly, partly because of the increased use of combination therapy for refractory seizure disorders and the increased use of these drugs for nonseizure indications, such as neuropathic pain, migraine headache prevention, and certain psychiatric conditions (e.g., bipolar disorder). This trend is expected to continue because pipeline anticonvulsants are also being studied for nonseizure indications.

New anticonvulsants
Several new antiseizure agents are expected to reach the market in 2009 for adjunctive use in treating seizure disorders. Vigabatrin is a novel anticonvulsant with potential indications for complex partial seizures and infantile spasms. However, because vigabatrin has been linked to an increased risk of visual defects, it is likely to be reserved for refractory cases. Retigabine, a gamma-aminobutyric acid and potassium channel agonist, has a unique mechanism of action. Carisbamate, an agent similar to Topamax, is expected in late 2009, several months after Topamax loses patent protection. Both retigabine and carisbamate are being studied for seizures and neuropathic pain. Also expected in 2009 is Lamictal® XR, which may offer increased patient convenience through once-daily dosing. However, this new dosage form could reduce potential savings from generic versions of lamotrigine immediate release, which entered the market in 2008.
First-time generics
Unit-cost growth of antiseizure agents will be significantly moderated by the continued infiltration of generics into this category. First-time generics for Depakote® (divalproex), Keppra® (levetiracetam), and Lamictal® (lamotrigine) were approved in 2008. Additional first-time generics are expected in early 2009 when patents expire on Depakote® ER (divalproex extended release) and Topamax (topiramate). Combined, these five branded antiseizure medications accounted for approximately $6.3 billion in U.S. sales in 2008. However, new products and anti-generic substitution initiatives at the state level represent threats to these savings.

ANTIDEPRESSANTS
Overall utilization of antidepressants is likely to grow slowly over the next 3 years. Although they lack clear evidence of superiority over other antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs) are likely to generate most of the growth in the category. Growth is also expected to come from patients with fibromyalgia syndrome (FMS), a chronic pain syndrome often accompanied by depression. FMS affects approximately 1% to 5% of the U.S. population. In 2008, Cymbalta and Savella™ were both approved for symptoms related to FMS. Continued use of SNRIs for FMS and for neuropathic, lower-back, and osteoarthritis pain and other indications may fuel utilization growth in this category as patients migrate from other agents used for pain to these agents. A supplemental NDA for use of Cymbalta to treat osteoarthritis pain and chronic lower back pain is expected in mid 2009. Approval of these two indications will make Cymbalta a major competitor in the pain management marketplace.

New antidepressants
Several novel antidepressants are in the pipeline. Saredutant is a neurokinin-2 receptor blocker with antidepressant and antianxiety properties. It may reach the market in 2009. Agomelatine, also expected in 2009, is a melatonin agonist/serotonin antagonist that may have beneficial effects on sleep patterns. These agents have novel mechanisms of action but have not yet been shown to be more effective than currently available antidepressants. Vilazodone, expected in 2011, is an SSRI-like antidepressant which is being developed with a companion diagnostic test that identifies patients most likely to respond to therapy.

Generic antidepressants
Unit-cost growth among antidepressants is expected to be moderated by potential savings in the SSRI category. Utilization of SSRIs is likely to remain flat, but unit cost is likely to decline because the SSRI category is now predominantly generic. Lexapro® (escitalopram), the last remaining branded SSRI, is expected to lose patent after 2012. However, first-time generics for Effexor XR (venlafaxine extended release), an SNRI that accounted for $2.79 billion in drug spending in 2008, may reach the market in late 2010.

ANTIPSYCHOTICS
Atypical antipsychotics are expected to show high single-digit utilization growth over the next 3 years. In addition to being used to treat schizophrenia, many of these drugs are also approved for short- and long-term treatment of mania associated with bipolar disorder. Seroquel XR®, which was approved in 2008, may win approval for indications in major depressive disorder and generalized anxiety disorder in the next year or two. Off-label uses for these drugs include obsessive-compulsive disorder, post-traumatic stress disorder, personality disorders, and dementia. A recent warning about use of these drugs in the elderly with dementia does not appear to have significantly dampened their use.

New antipsychotics
Iloperidone is being co-developed with a diagnostic test to identify a genetic variation that occurs in approximately 70% of patients and may be associated with a better response to the drug. After failing to win FDA approval in 2008 because of efficacy concerns, iloperidone was resubmitted and a decision is expected in 2009. Asenapine (Saphris®) (also expected in 2009) is a sublingual, twice-daily atypical antipsychotic being developed for schizophrenia and bipolar disorder. Asenapine appears to have similar efficacy to Zyprexa® but may cause less weight gain. In January 2009, the FDA requested additional information on this drug before approval could be granted.
First-time generics

First time generics for Risperdal® (risperidone) were introduced in mid 2008. In the first quarter of 2008, Risperdal held 21.5% of the antipsychotic market by prescription volume, but at the end of the fourth quarter, it held only 3.27% of the antipsychotic market, the balance being captured by generics. The availability of generic risperidone is expected to somewhat moderate unit-cost growth for antipsychotics over the next few years. Also, first-time generics for Zyprexa could reach the market in 2011.

MULTIPLE SCLEROSIS (MS)

Along with a new version of interferon beta-1b being developed by Novartis, several new oral drugs for MS are being developed and may reach the market in 2010. These agents should have an advantage over interferons, which are administered as injections and are generally poorly tolerated. The drugs in the pipeline for MS include:

- Sustained-release fampridine (4-aminopyridine) blocks potassium channels in nerves and is being studied to increase walking speed in patients with more advanced MS.
- Fingolimod, a once-daily oral immunosuppressant lowers the levels of activated T-cells in the bloodstream and in the CNS.
- An oral formulation of cladribine, expected in 2010; cladribine, a chemotherapeutic agent, has been used off-label as a treatment for MS, but currently it must be given by intravenous or subcutaneous injection.

All these agents will join the other specialty drugs for the treatment of MS, leading to increased costs in the category. However, newer drugs will be challenged to displace existing therapies that have good long-term safety and efficacy data. Also, the initial data on these newer drugs suggest that they carry significant risks of immunosuppression. Thus, movement away from existing agents in this category will likely be slow.

NONNARCOTIC PAIN RELIEVERS

Use of nonnarcotic analgesics has declined dramatically in recent years in response to evidence that cyclo-oxygenase-2 (COX-2) inhibitors, and possibly all NSAIDs, are associated with increased cardiovascular risk. Celecoxib (Celebrex®) remains the only available COX-2 inhibitor on the market. No other COX-2 inhibitors are in development, but the following products are being developed to help protect against NSAID-induced gastrointestinal toxicity and are expected in 2010: an ibuprofen/famotidine combination, a naproxen/esomeprazole combination, and naproxcinod, a novel form of naproxen that releases nitric oxide in the gastointestinal tract. Naproxcinod may protect against NSAID-induced ulcers and may also have a less detrimental effect on blood pressure than other NSAIDs. Moderate utilization growth for the nonnarcotic analgesics will probably continue over the next 3 years, tempered by unit-cost savings from an all-generic NSAID class.

NARCOTIC PAIN RELIEVERS

Utilization of narcotic pain relievers is likely to increase by about 5% per year over the next 3 years. Products in the pipeline include reformulations of currently available narcotics that are designed to have a lower risk for abuse or misuse. Several of these products could reach the market in 2009. Remoxy® is a new extended-release version of oxycodone formulated as a gel cap that appears to be resistant to dissolution with alcohol and cannot be crushed. Embeda™ contains morphine sulfate and naltrexone (a morphine antagonist); crushing of Embeda releases naltrexone from the bead cores, thus blocking the effects of morphine. Acurox® contains oxycodone and subtherapeutic amounts of niacin; if the product is crushed, the released niacin produces unpleasant adverse effects such as flushing, headache, and itching. Finally, Oxytrex™, anticipated in 2010, is a new formulation of oxycodone that contains ultra-low doses of naltrexone, which may reduce development of tolerance to the effects of oxycodone.

These new, single-source formulations of existing narcotics are expected to contribute to sustained increases in unit cost over the next 3 years. However, none of them are expected to provide a significant advantage over currently available narcotic pain relievers.
Finally, tapentadol, a nonnarcotic analgesic, was approved in 2008 but is awaiting a decision from the Drug Enforcement Administration (DEA) on controlled substance scheduling. Tapentadol is expected to enter the market sometime in 2009 and could face stiff competition from generic tramadol products. The final DEA scheduling of this drug will likely influence its success.

**Fate of propoxyphene unclear**

The FDA held an Advisory Committee meeting in early 2009 to discuss the risk-benefit ratio of propoxyphene-containing products (*Darvocet®, Darvon®, and generics*). These products generated approximately 20 million prescriptions and $522 million in drug expenditures in 2008. If propoxyphene were removed from the market, patients would probably switch to other mild narcotic combinations (acetaminophen/codeine), weak opioids such as tramadol, or more expensive branded products such as tapentadol. If the FDA takes this action, it will likely involve a gradual marketplace withdrawal.

**First-time generics**

After a brief period when generic versions of *OxyContin®* (oxycodone) were available, patent litigation and settlements between the brand and generic manufacturers have resulted in a diminished supply of generics and the reemergence of the *OxyContin* brand.47 *OxyContin* is once again among the market share leaders in the narcotic category, responsible for over $2 billion in drug expenditures in 2008.45 Generics for *OxyContin* are not expected to reenter the market until the patent expires in 2013. The only new generic narcotic on the horizon is a generic version of *Kadian®* (morphine extended release), which may lose patent protection in 2010.

**MIGRAINE**

Approximately 17% of women and 5% of men between 12 and 80 years of age experience migraine headaches.48 Triptans are commonly used to abort acute migraine attacks. *Imitrex* (sumatriptan tablets), the triptan with the largest market share in this class by prescription volume and sales (approximately $1 billion in 2008), is expected to become available as a true generic in early 2009.45 Availability of generic sumatriptan is expected to moderate unit-cost growth in the triptan category over the next 3 years. However, talcagepant (expected in 2010) is a calcitonin gene related peptide (CGRP) receptor antagonist that will be the first in a new class of agents since triptans. Whether talcagepant will be used alone or with a triptan is still unclear. However, a new class of drugs in this category will contribute to utilization and cost growth.

**ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)**

Approximately 7.8% of U.S. school-aged children (4 to 17 years of age) have received an ADHD diagnosis, and about 4.3% of children currently take drugs for this condition.49 Approximately 4.4% of adults aged 18 to 44 have ADHD, but only 1.2% of them are currently taking drugs for this disorder.49–50 Guanfacine, which was formerly indicated for hypertension and has been on the market for 20 years, is being reformulated as an extended-release drug for ADHD in both adults and children. If approved, guanfacine will be the second nonstimulant drug indicated for ADHD. *Adderall XR* (mixed amphetamines sustained release) is expected to lose patent protection in early 2009, when an authorized generic may become available. *Adderall XR* accounted for over $1.5 billion in drug expenditures in the category during 2008.45

**ALZHEIMER’S DISEASE**

Utilization of drugs for Alzheimer’s disease continues to grow at a rate of about 6% per year, reflecting increased combination use of *Aricept* and *Namenda®*. Several disease-modifying pipeline drugs have recently been discontinued because of disappointing efficacy results. However, bapineuzumab, a monoclonal antibody targeted against beta-amyloid, has shown promise, especially in patients without a specific genetic marker, APOE4. Bapineuzumab could reach the market in 2011, perhaps with use limited to the APOE4 population. First-time generics for *Aricept* (donepezil) could be introduced sometime in the next 3 years. Some *Aricept* patents are scheduled to expire in 2010, but generics may be available earlier, depending on the results of ongoing patent litigation. Generic versions of *Aricept* could result in substantial savings for plans; the drug accounted for approximately $1.2 billion in sales in 2008 and is the most popular of the cholinesterase inhibitors.45
SEDATIVE-HYPNOTICS

No new insomnia treatments were approved by the FDA in 2008, and generic versions of zolpidem (Ambien®), which rapidly captured over 50% of the market share in 2007, continued to lead the market in 2008, resulting in substantial savings for plans able to capitalize on this generic opportunity. First-time generics for Ambien CR® (zolpidem controlled release), which accounted for almost $1 billion in drug expenditures in 2008, are expected in early 2009.45 Silenor® (doxepin extended release), a reformulated antidepressant, may be introduced in 2009 as a treatment for insomnia. Silenor does not work on the benzodiazepine receptor and is unlikely to be designated a controlled substance, a potential advantage. Although several pipeline hypnotics, such as tasimelteon, eplivanserin, and indiplon, may be approved in the next 3 years, none appears to have a clear advantage over generic zolpidem. Sustained momentum toward generic hypnotics in the category is expected to moderate trend growth in other areas. Some ambulatory-use CNS drugs in the pipeline are listed in Table 7.

Table 7. Some ambulatory-use CNS agents in the pipeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Generic name</th>
<th>Uses</th>
<th>Potential impact on drug trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>asenapine</td>
<td>Schizophrenia, bipolar disorder</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>guanfacine extended release</td>
<td>Attention deficit hyperactivity disorder</td>
<td>$</td>
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<td></td>
<td>iloperidone</td>
<td>Schizophrenia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>lamotrigine extended release</td>
<td>Seizure disorders, bipolar disorder</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>morphine extended release + naltrexone</td>
<td>Chronic pain</td>
<td>$</td>
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<tr>
<td></td>
<td>oxycodone extended release (abuse-resistant formulation)</td>
<td>Chronic pain</td>
<td>$</td>
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<td></td>
<td>oxycodone + niacin</td>
<td>Insomnia</td>
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<tr>
<td></td>
<td>vigabatrin</td>
<td>Infantile spasms, Lennox-gastaut</td>
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<td></td>
<td>retigabine</td>
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<td></td>
<td>sertindole</td>
<td>Schizophrenia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>carisbamate</td>
<td>Seizure disorders</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>indiplon</td>
<td>Insomnia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>agomelatine</td>
<td>Depression</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>tasimelteon</td>
<td>Insomnia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>eplivanserin</td>
<td>Insomnia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>saredutant</td>
<td>Depression</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ketorolac intranasal</td>
<td>Pain</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>fampridine sustained release</td>
<td>Multiple sclerosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>cladribine (oral)</td>
<td>Multiple sclerosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>laquinimod</td>
<td>Multiple sclerosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>fingolimod</td>
<td>Multiple sclerosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>tecfidera</td>
<td>Multiple sclerosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>naproxen</td>
<td>Osteoarthritis</td>
<td>$§</td>
</tr>
<tr>
<td></td>
<td>pamidronate</td>
<td>Parkinson’s disease</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>nizatidine</td>
<td>Parkinson’s disease</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ibuprofen + famotidine</td>
<td>Mild-to-moderate pain</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>gabapentin extended release</td>
<td>Seizure disorders, neuropathic pain</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>naproxen + esomeprazole</td>
<td>Pain</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>eslicarbazepine</td>
<td>Seizure disorders</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>carisbamate</td>
<td>Multiple sclerosis</td>
<td>$</td>
</tr>
<tr>
<td>2011</td>
<td>dirucotide</td>
<td>Multiple sclerosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>vilazodone</td>
<td>Depression</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>baxinuzumab</td>
<td>Alzheimer’s disease</td>
<td>$§</td>
</tr>
<tr>
<td></td>
<td>BG-12</td>
<td>Multiple sclerosis</td>
<td>$</td>
</tr>
</tbody>
</table>

$§ = potential to cause a ≥2% increase in this category’s trend.
$ = potential to cause a <2% increase in this category’s trend.
Bold text indicates potential specialty drugs.
Endocrine and diabetes agents

Contribution to plan spending (2008): 8%
Projected contribution to trend (2009 to 2011): 18%

Projected trend

Table 8. Drug trend projection for endocrine and diabetes agents*

<table>
<thead>
<tr>
<th>Year</th>
<th>Utilization increase</th>
<th>Price and mix increase</th>
<th>Annual total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>1% to 2%</td>
<td>9% to 10%</td>
<td>10% to 12%</td>
</tr>
<tr>
<td>2010</td>
<td>1% to 2%</td>
<td>7% to 8%</td>
<td>8% to 10%</td>
</tr>
<tr>
<td>2011</td>
<td>1% to 2%</td>
<td>9% to 10%</td>
<td>10% to 12%</td>
</tr>
</tbody>
</table>

*T:Projected change in drug spending on a plan ingredient cost PMPY basis

TREND PREDICTIONS

Key developments that are likely to shape drug trend in the endocrine and diabetes category over the next 3 years:

- Continued rapid growth in utilization of diabetes drugs because of the epidemic of obesity and diabetes in this country
- Increased use of multiple-drug therapy to help control blood glucose levels and prevent long-term complications of diabetes
- Introduction of several new oral and injectable agents for the treatment of diabetes and its complications
- Very limited first-time generic introductions

Trend drivers: New users of oral hypoglycemic agents, insulin products
Trend moderators: None

DIABETES

Obesity and diabetes

The diabetes epidemic continues to grow. Recently the Centers for Disease Control (CDC) estimated that the incidence of diabetes in the United States has more than doubled in the last 15 years to almost 24 million people.53 Diabetes has been diagnosed in 18 million people and remains undiagnosed in an estimated 5.7 million. Moreover, the CDC projects that another 57 million Americans have prediabetes, placing them at high risk for developing type 2 diabetes.55 Fifty-seven million people with prediabetes represent an enormous future burden on our healthcare system. Dietary modifications and regular exercise can delay or prevent the development of diabetes in these people, but these lifestyle changes are difficult to follow consistently. As a result, obesity-related onset of diabetes is likely to be a major contributor to the rapid utilization growth of diabetes drugs over the next several years.
The increase in diabetes prevalence is attributable largely to the epidemic of obesity in the United States. Nearly 9 out of 10 people with newly diagnosed type 2 diabetes are overweight. The potential future increase in the number of patients with diabetes is overwhelming. During the period 2003–2004, about 67% of adults aged 20 to 74 were overweight and 34% were considered obese. When similar criteria are used, almost 18% of children and adolescents aged 6 to 19 are overweight or obese.

In spite of the availability of numerous drugs to help treat diabetes, only a fraction of patients with the disorder achieve their target goals for blood glucose, cholesterol, and blood pressure. The remaining patients represent an undertreated population that will accelerate future utilization growth for diabetes drugs—including oral and injectable hypoglycemic agents, insulin products, and drugs for diabetes complications.

**Tighter control**
Combinations of oral agents are being used more frequently to help patients reach aggressive hemoglobin A1c targets, such as the 6.5% level recommended by the American College of Endocrinology, or 7% level recommended by ADA. Two- and three-drug combinations are frequently required to help patients achieve adequate blood glucose control. A long-term clinical trial recently indicated that tight control of blood glucose levels may reduce the macrovascular, as well as microvascular, complications of type 1 diabetes.

In spite of the anticipated benefits from lowering the hemoglobin A1c levels of diabetic patients to those of nondiabetics, a recent study in type 2 diabetics was halted early because of an increased risk of death among patients who were aggressively managing their A1c levels to below 6%. The researchers have been unable to identify any specific cause for the higher death rate among the intensively treated group. Two other recent studies have also reported a similar lack of benefit from aggressively lowering blood glucose levels in patients with diabetes. Thus, physicians may be reluctant to lower their patients’ A1c levels below 6.5% or 7% until more clinical data are available. Today, most patients with diabetes do not achieve A1c levels below 7%, so progress is still required in terms of improving their glycemic control.

**New drugs in development and the new FDA guidance**
Several new pipeline drugs for the treatment of type 2 diabetes may be approved over the next several years. However, the timing of these approvals hinges on how the FDA applies recent guidance for drugs to treat diabetes, which includes the need to evaluate the cardiovascular risk associated with these drugs.

This new guidance significantly increases the number of patients who must be exposed to the drug under development and also requires inclusion of high-cardiovascular-risk patients in clinical trials.

**Inhaled insulin**
Mannkind has the only remaining inhaled insulin under clinical development. Although it may receive FDA approval in late 2010 or early 2011, the actual launch date depends on the company’s ability to find a marketing partner.

**New injectables: Glucagon-like peptide-1 agonists**
Glucagon-like peptide-1 agonists have multiple effects on blood glucose control. They stimulate the secretion of insulin in the presence of elevated blood glucose, slow gastric emptying, and inhibit secretion of glucagon. Over time, the use of these drugs often leads to weight loss—an unusual benefit among drugs for diabetes.
A new injectable agent, liraglutide, is under FDA review for the treatment of type 2 diabetes. Liraglutide acts similarly to Byetta® (exenatide) in reducing A1C levels and weight but is administered only once daily. A once-weekly dosage form of exenatide is also in clinical development and could be approved in late 2010 or early 2011. A once-weekly injectable for the treatment of diabetes would be a revolutionary advance and would probably enjoy widespread utilization.

**Oral drugs: Dipeptidyl peptidase IV (DPP-IV) inhibitors**

DPP-IV inhibitors are likely to be used in multiple-drug combinations for patients with diabetes. For example, a new combination product containing sitagliptin and metformin (Janumet®) was approved in March 2007. Several additional DPP-IV inhibitors and DPP-IV combination products are in late-stage clinical development and may be approved over the next 3 years, including alogliptin, saxagliptin, vildagliptin, and vildagliptin/metformin.

Some ambulatory-use endocrine and diabetes drugs in the pipeline are listed in Table 9.

### Table 9. Some ambulatory-use endocrine and diabetes agents in the pipeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Generic name</th>
<th>Uses</th>
<th>Potential impact on drug trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>alogliptin</td>
<td>Type 2 diabetes</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>liraglutide</td>
<td>Type 2 diabetes</td>
<td>$</td>
</tr>
<tr>
<td>2010</td>
<td>valsartan + nateglinide</td>
<td>Reduction in risk for new-onset type 2 diabetes</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>saxagliptin</td>
<td>Type 2 diabetes</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>exenatide long-acting formulation</td>
<td>Type 2 diabetes</td>
<td>$</td>
</tr>
<tr>
<td>2011</td>
<td>vildagliptin</td>
<td>Type 2 diabetes</td>
<td>$</td>
</tr>
</tbody>
</table>

$ = potential to cause a <2% increase in this category's trend.  
$$ = potential to cause a >2% increase in this category's trend.
Musculoskeletal and rheumatological agents

Contribution to plan spending (2008): 5.0 %
Projected contribution to trend (2008 to 2010): 14 %

Projected trend

Table 10. Drug trend projection for musculoskeletal and rheumatological agents*

<table>
<thead>
<tr>
<th>Year</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Utilization increase</td>
<td>0% to 1%</td>
<td>4% to 5%</td>
</tr>
<tr>
<td></td>
<td>Price and mix increase</td>
<td>7% to 8%</td>
<td>9% to 10%</td>
</tr>
<tr>
<td></td>
<td>Annual total</td>
<td>7% to 9%</td>
<td>13% to 15%</td>
</tr>
</tbody>
</table>

*Trend predictions

Key developments that are likely to shape drug trend for musculoskeletal and rheumatological drugs over the next 3 years:

- Introduction of interleukin-6 antagonism as a new treatment strategy for RA
- Increased use of both existing and pipeline biologics, such as Enbrel®, Humira®, Orencia®, Rituxan®, golimumab, and tocilizumab, for the treatment of RA
- Introduction of novel drugs for the treatment of gout, including at least one new high-cost injectable biologic agent
- Introduction of denosumab for the treatment and prevention of osteoporosis, as well as for use in reducing the risk of skeletal events in patients with metastatic cancer
- Multiple new selective estrogen-receptor modulators (SERMs) for the treatment/prevention of osteoporosis and the prevention of breast cancer
- Introduction of one or more new injectable biologics for the treatment of SLE

Trend drivers: New biologics for RA and new drugs for the treatment of osteoporosis, gout, and SLE
Trend moderator: Generics for Fosamax and Fosamax Plus D® gaining market share

OSTEOPOROSIS

Treatment trends

An estimated 44 million Americans have been diagnosed with or at risk of developing osteoporosis. Plan spending for this treatment class is expected to be relatively flat in 2009 because generics for alendronate (Fosamax) are gaining ground. However, spending will increase with the 2010 introduction of denosumab, a twice-yearly subcutaneously administered biologic. New SERMs for the treatment and prevention of osteoporosis will also contribute to increased spending in the category starting in 2010.

Once-weekly and once monthly oral bisphosphonates, such as alendronate (Fosamax), Boniva®, and Actonel®, continue to account for over three-fourths of total utilization among osteoporosis drugs, with alendronate still the market leader. Concerns over bisphosphonate-induced osteonecrosis of the jaw (ONJ) may be partially responsible for the flat to slightly declining use of these drugs, but the risk of ONJ is more clearly associated with intravenous bisphosphonates. No new oral bisphosphonates appear to be in the near-term pipeline.
Evista®, Miocalcin®, Fortical®, and Forteo® are also used to treat osteoporosis, but these drugs account for a much smaller share of overall utilization. Among marketed and pipeline drugs for the treatment or prevention of osteoporosis, Forteo is the only one that increases osteoblast activity and can actively build new bone, making it an attractive choice in patients at very high risk for fractures. Forteo has been shown to increase bone mineral density (BMD) to a greater extent than alendronate in patients with glucocorticoid-induced osteoporosis. However, the need for once-daily subcutaneous administration of Forteo and the 2-year limit on its use, mostly because of theoretical concern over osteogenic sarcoma, appear to continue to curtail utilization.

SERMs: A rich pipeline, but unclear advantages in osteoporosis
SERMs are drugs that have estrogen-like beneficial effects on bone and lipid profiles but antagonize estrogen’s effects on reproductive tissues, such as those of the breast and uterus. Evista was the first SERM to win FDA approval, and it is now also approved for use in reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis or women at increased risk for breast cancer. This new indication—preventing breast cancer—may have contributed to the increasing market share of Evista among osteoporosis drugs over the past year.

In September 2008, an FDA Advisory Committee recommended approval of a second SERM, lasofoxifene, for the treatment of osteoporosis in certain postmenopausal women who are at high risk and cannot tolerate other therapies. Despite this recommendation, the FDA requested additional information on this drug in January 2009. Therefore, lasofoxifene will face additional delay before FDA approval. The impact of this new compound in the osteoporosis market is expected to be modest because SERMs are generally less favored than bisphosphonates.

Two additional pipeline SERMs, bazedoxifene and arzoxifene, are also in late-stage clinical development. Approval of bazedoxifene is possible in 2009, and a combination product containing bazedoxifene and conjugated estrogens may be approved in 2010. Thus far, bazedoxifene has garnered two approvable letters from the FDA, but concerns about a possible increased risk of stroke and thromboembolic events will likely contribute to a delay for this drug. The combination product of bazedoxifene with conjugated estrogens may help minimize endometrial thickening caused by conjugated estrogen while alleviating postmenopausal symptoms that might be worsened by bazedoxifene alone.

The third new SERM, arzoxifene, a compound very closely related to Evista, is being studied for the treatment of osteoporosis and for the prevention and treatment of breast cancer. The studies evaluating arzoxifene for osteoporosis are scheduled to conclude in 2010 and the drug could come to market in 2011. Whether these newer compounds will outperform Evista in terms of fracture reduction or breast cancer risk reduction is unclear. However, if they all eventually come to market, the SERM category will become crowded like the bisphosphonate category and could garner additional market share.

Other new drugs
Odanacatib is being studied in Phase III trials for the treatment and prevention of osteoporosis. This is the first drug to inhibit cathepsin K, which is found on osteoclasts, the cells involved in the breakdown of bone. It is too early to judge how odanacatib will perform relative to bisphosphonates. It will probably not be introduced before 2012.

New biologic drugs for osteoporosis
A new monoclonal antibody for the treatment and prevention of osteoporosis, denosumab, may be introduced in 2010. Denosumab inhibits the activity of osteoclasts, the cells responsible for breakdown of bone, by inhibiting the activation of the nuclear factor kappa B pathway. Published data suggest that denosumab may equal or surpass Fosamax in increasing BMD. Additionally, data from a recent study suggest that denosumab is effective in increasing BMD in patients with breast cancer who are undergoing treatment with antiestrogen agents known to accelerate bone loss and increase fracture risk. This would be another new indication for a drug in the osteoporosis category.
The manufacturer of denosumab is also seeking an indication to reduce the risk of skeletal events in patients with breast and prostate cancer who already have bony metastasis. Approval of denosumab for this indication would allow it to compete directly with zolendronic acid (Reclast®), which is already approved for this use. Denosumab is also being studied for reducing the risk of first bony metastasis in patients with metastatic prostate cancer that has not yet infiltrated the bone. This use represents a significant market opportunity for denosumab, and one in which there are currently no other FDA-approved products.

Denosumab is self-administered by subcutaneous injection only twice yearly, so it could be well accepted by patients and prescribers, especially if it proves to be well tolerated. Whether the fracture risk reduction with denosumab will rival that with the bisphosphonates remains to be determined, but the available data suggest that this drug can increase BMD as much as or more than alendronate. Use of denosumab may not pose the risk of ONJ associated with bisphosphonates, and, unlike bisphosphonates, it does not accumulate in bone and therefore its effects are shorter lived.

A once-yearly injectable formulation of zoledronic acid was approved in 2007 for the treatment of osteoporosis. Once-yearly administration combined with impressive data for fracture risk reduction continues to make this drug an attractive option for patients who are candidates for bisphosphate therapy. This same drug marketed under the brand name Zometa® has shown good results in reducing the risk of skeletal-related events in patients with metastatic cancer. Recently, use of this drug added to adjuvant endocrine therapy has also been shown to improve disease-free survival in premenopausal women with estrogen-responsive early breast cancer. Therefore, Reclast could soon become the standard of care in many or all patients with metastatic breast cancer. This would be a significant new use for an injectable bisphosphonate.

First-time generics
Generic versions of Fosamax (alendronate) were introduced in early 2008, and generics for Fosamax Plus D are expected in 2009. Other generics in this category are not expected until after 2011. These new generics will continue to lower unit costs in the class as their market share increases. However, this favorable trend could be reversed once denosumab comes to market. As a novel biologic, this product will likely be a costly alternative to bisphosphonates.

RHEUMATOID ARTHRITIS (RA)

Treatment trends
Rheumatoid arthritis (RA) is a common condition affecting more than 2 million Americans, many of whom are candidates for treatment with an existing biologic agent, such as Enbrel, Humira, or Rituxan. These biologic agents have the potential to achieve disease remission to an extent not previously possible.

Biologics are being used much earlier and more frequently in RA treatment, as results from clinical trials continue to demonstrate their excellent efficacy and safety profiles. The American College of Rheumatology recommends the use of TNF inhibitors to treat newly diagnosed RA in patients with high disease activity or those with longer-duration RA who have had an inadequate response to methotrexate. For patients who do not respond to TNF inhibitors, Orencia and Rituxan are other options.

New indications for biologics
Orencia was recently approved as a first-line treatment for RA. However, TNF inhibitors will generally be tried first because some can be self-administered and these drugs have longer-term safety data. Humira is also being studied for use in treating ulcerative colitis. FDA approval for this indication is expected in the next year or two. If Cimzia®, which won approval in 2008 for the treatment of Crohn’s disease, also wins approval for use in RA, there will be at least six distinct biologic agents that are FDA approved for the treatment of this condition.
New specialty drugs for RA

Several new biologics are in the near-term pipeline for RA:

- Golimumab, a fully humanized monoclonal anti-TNF antibody that may be introduced in 2009 and could be available in both intravenous and subcutaneous dosage forms, is in clinical development for RA, psoriatic arthritis, and ankylosing spondylitis. The subcutaneous dosage form could be dosed just once every 4 weeks and the intravenous dosage form every 12 weeks.

- Treatment of immune-mediated diseases by inhibiting various interleukins is an active area of new drug development. Tocilizumab, an intravenously administered anti-interleukin-6-receptor monoclonal antibody in clinical development for RA, could be introduced in 2009. FDA approval appears to be dependent on an acceptable REMS program. In January 2009, tocilizumab was approved for use in Europe for the treatment of RA in patients who could not tolerate other disease-modifying antirheumatic drugs. This drug will likely be used mostly as a second-line agent for patients in whom other TNF inhibitors have failed.

Novel drugs for gout

Gout is a form of arthritis that affects mostly men. The symptoms are caused by the collection of urate crystals in the joints, which is very painful and can lead to joint destruction. In the United States, the reported prevalence of gout is about 1.4% in males and 0.6% in females; prevalence increases with age. Allopurinol, which decreases uric acid production, has been used for decades to prevent gout. About 12 million prescriptions were written for allopurinol in the United States during 2008.

After years of delay, in November 2008, an FDA Advisory Board recommended approval of febuxostat (Uloric®), another xanthine oxidase-inhibiting drug like allopurinol, and the FDA approved it in February 2009. Febuxostat is the first new drug for the prevention of gout in decades. It appears to be more effective than allopurinol in lowering uric acid levels and also can be used in patients with renal failure, in whom allopurinol is generally less effective. As a new single-source drug in an all-generic category, febuxostat could add significantly to unit cost but not very much to utilization, because it will probably be used in place of allopurinol.

For patients with gout in whom all other agents have failed, a new biologic agent is also on the horizon. Pegloticase recently received a priority review status from FDA with a user end date of July 2009. This intravenous drug is an enzyme, urate oxidase, which breaks down uric acid into a harmless substance. The enzyme is pegylated to prolong its duration of action. Introduction of pegloticase into the marketplace will move treatment of refractory gout into the high-cost specialty arena and could contribute to rising cost in an area that has long been dominated by generics.

New treatment for systemic lupus erythematosus (SLE)

SLE is a chronic relapsing and remitting autoimmune disorder that affects mostly women. The disease, which has no cure, causes damage to a variety of body organs, including skin, heart, joints, blood vessels, and kidneys. Current treatments, which are aimed at reducing disease flares, include a variety of immunosuppressive drugs that are used off-label, such as corticosteroids, azathioprine, and Rituxan.

There has not been a new drug for the treatment of SLE in many years, but several potentially high-cost specialty or biologic agents for the treatment of SLE are in the pipeline, including:

- Ocrelizumab, an intravenously administered humanized anti-CD 20 monoclonal antibody that recruits the body’s immune system to attack and destroy B-cells. This drug is being studied in Phase III trials for lupus nephritis, the renal complication of SLE.

- Belimumab, an intravenously administered monoclonal antibody that inhibits the biologic activity of the protein B-lymphocyte stimulator (BlyS). BlyS is necessary for the maturation of B-cells into antibody-producing cells. Elevated levels of BlyS occur in patients with SLE, perhaps increasing self-antibody production and disease activity. By blocking this protein, belimumab may reduce the signs and symptoms of SLE.

- Epratuzumab, an intravenous monoclonal antibody directed against the CD-22 antigen on B-lymphocytes. Similar to belimumab, epratuzumab is aimed at decreasing antibody production that may be involved in the pathogenesis of SLE.
If approved, these high-cost biologics for the treatment of SLE will add to costs and utilization in the rheumatological drug category.

Examples of ambulatory-use musculoskeletal and rheumatological drugs in the pipeline are listed in Table 11.

Table 11. Some ambulatory-use musculoskeletal and rheumatological agents in the pipeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Generic name</th>
<th>Uses</th>
<th>Potential impact on drug trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>bazedoxifene</td>
<td>Osteoporosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>lasofoxifene</td>
<td>Osteoporosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>tocilizumab</td>
<td>Rheumatoid arthritis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>golumimab</td>
<td>Rheumatoid arthritis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>pegloticase</td>
<td>Gout</td>
<td>$§</td>
</tr>
<tr>
<td></td>
<td>bazedoxifene + conjugated estrogen</td>
<td>Osteoporosis, postmenopausal symptoms</td>
<td>$§</td>
</tr>
<tr>
<td>2010</td>
<td>denosumab</td>
<td>Osteoporosis</td>
<td>$§</td>
</tr>
<tr>
<td></td>
<td>abatacept (subcutaneous formulation)</td>
<td>Rheumatoid arthritis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>belimumab</td>
<td>Lupus erythematosus</td>
<td>$</td>
</tr>
<tr>
<td>2011</td>
<td>odanacatib</td>
<td>Osteoporosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>arzoxifene</td>
<td>Osteoporosis, breast cancer</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ospemifene</td>
<td>Vaginal atrophy</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>epratuzumab</td>
<td>Systemic lupus erythematosus</td>
<td>$§</td>
</tr>
<tr>
<td></td>
<td>clodronate</td>
<td>Bone metastasis in breast cancer, hypercalcemia of malignancy</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ocrelizumab</td>
<td>Lupus nephritis</td>
<td>$</td>
</tr>
</tbody>
</table>

$§ = potential to cause a <2% increase in this category's trend.
$ = potential to cause a 2-12% increase in this category's trend.
Bold text indicates potential specialty drugs.
Respiratory agents

Contribution to plan spending (2008): 8%
Projected contribution to trend (2009 to 2011): 8%

Projected trend

Table 12. Drug trend projection for respiratory agents*

<table>
<thead>
<tr>
<th>Year</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utilization increase</td>
<td>0% to 1%</td>
<td>0% to 1%</td>
<td>0% to 1%</td>
</tr>
<tr>
<td>Price and mix increase</td>
<td>1% to 2%</td>
<td>6% to 7%</td>
<td>7% to 8%</td>
</tr>
<tr>
<td>Annual total</td>
<td>1% to 3%</td>
<td>6% to 8%</td>
<td>7% to 9%</td>
</tr>
</tbody>
</table>

*Projected change in drug spending on a plan ingredient cost PMPY basis

TREND PREDICTIONS

Key developments that are likely to shape drug trend in the respiratory category over the next 3 years:
- New corticosteroid/long-acting bronchodilators combination products to compete with Advair Diskus®
- Phase-out of chlorofluorocarbon (CFC) metered-dose inhalers and replacement with single-source branded hydrofluoroalkane (HFA) inhalers
- New treatments for hereditary angioedema (HAE), pulmonary arterial hypertension, and cystic fibrosis
- Conversion of desloratadine (Clarinex) to OTC status

Trend driver: New treatments for pulmonary diseases
Trend moderator: Nonsedating antihistamines

ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Treatment trends
The use of single-entity long-acting bronchodilators, such as Serevent® Diskus® and Foradil®, has continued to decline in recent years in response to concerns about an increased risk of mortality associated with these drugs in the treatment of asthma.65,66 Long-acting beta-agonists are not recommended for asthma monotherapy but are recommended for use in combination with inhaled corticosteroids in moderate-to-severe persistent asthma.65 The FDA has advised healthcare professionals to prescribe inhaled corticosteroids as first-line controller therapy and to add long-acting bronchodilators only if inhaled steroids are inadequate to achieve control or if dual therapy is required because of the severity of the asthma.

New treatments for COPD
New products will contribute to unit-cost and utilization growth for asthma/COPD controller medications over the next 3 years. Despite the concerns about their safety, several long-acting beta-agonists are in development. Indacaterol, a once-daily, long-acting beta-agonist with a rapid onset of action (approximately 5 minutes), may be approved for asthma in 2009 and for COPD in 2010. Several inhaled corticosteroid/bronchodilator combinations and competitors for Advair® may reach the market in 2010. Flutiform® (fluticasone/formoterol) and mometasone/formoterol are being developed for the maintenance treatment of asthma and COPD. Acidinium, a new long-acting anticholinergic similar to Spiriva® (tiotropium), could reach the market in 2010. Roflumilast, a selective phosphodiesterase IV inhibitor with anti-inflammatory and vasodilation properties, has a novel mechanism and could reach the market in 2010 for the treatment of COPD.
First-time generics
No inhaled corticosteroid or inhaled corticosteroid combination products are expected to become available as generics during the next 3 years because of the current lack of bioequivalency standards for inhaled corticosteroids. Generic albuterol inhalers, which were available for many years, disappeared as the market transitioned from CFC-based to HFA-based inhalers in 2008. Single-source HFA-based inhalers have gained extended patent life because of the new propellant, and generic versions of these products will probably not be available until 2010 or later. Unit costs will increase as generic albuterol inhalers (based on CFC propellants) are replaced by new HFA-based inhalers.

PULMONARY ARTERIAL HYPERTENSION (PAH)

Treatment trends
Over the next several years, additional clinical data demonstrating the benefit of combination therapy for PAH should become available. Increased use of combination therapy will contribute to rising costs for treatment of this condition. In the past, most of the drugs used to treat PAH were administered parenterally and these expensive therapies were often billed under the medical benefit. However, as more oral drugs and inhaled medications to treat PAH become available, the costs of PAH treatment are likely to shift more to the pharmacy benefit.

New treatments
Viveta™, an inhaled formulation of treprostinil that is administered via portable nebulizer, is being developed for PAH and may be available by 2009. If approved, inhaled treprostinil, which is dosed four times daily, will have an advantage over Ventavis® (iloprost) inhalation, which requires six to nine inhalations per day. Also, Cialis® (tadalafil), a phosphodiesterase-IV inhibitor similar to Revatio® (sildenafil), is being studied as a treatment for PAH and could be approved in 2009.

ALLERGIC RHINITIS

In November 2007, Zyrtec and Zyrtec-D® (cetirizine) converted to OTC status, and use of prescription non-sedating antihistamines declined dramatically in 2008. During the first quarter of 2008, prescription volume for Zyrtec was about 13 million, but by the fourth quarter, prescription volume had fallen to only 22,000. First-time generics for Clarinex® (desloratadine) will probably become available in 2009; however, as was observed with other prescription antihistamines, this product may be converted to OTC status before the generic products are introduced. Utilization of prescription non-sedating antihistamines is expected to continue to decline over the next 3 years as patients migrate to OTC products.

CYSTIC FIBROSIS (CF)

Several new agents may be introduced for the treatment of CF over the next few years. These products will be used to control Pseudomonas infections, which are particularly common and problematic in this disease. Aztreonam inhalation (Cayston®), an antibiotic for administration via nebulizer, is expected in 2010. Cayston® may improve lung function and delay the need for other antibiotic treatments in CF patients with Pseudomonas aeruginosa infections in the lungs. A new dry-powder inhaler formulation of the antibiotic tobramycin may be available in 2010, also for the treatment of P aeruginosa lung infections. Tobramycin is already available for delivery via nebulizer, but a dry-powder inhaler would offer greater convenience and eliminate the need for a nebulizer. Finally, denufusol, a new drug that increases mucus hydration and clearance from the lungs, may come to market in 2011.

IDIOPATHIC PULMONARY FIBROSIS (IPF)

Pirfenidone, an oral agent that inhibits collagen synthesis, is being developed as a treatment for IPF, a rare, serious respiratory disorder. Actimmune® (interferon gamma-1b) had been used off-label as a treatment for this condition. However, in March 2007, the FDA issued an advisory that discouraged this off-label use because of safety concerns about Actimmune® that led to termination of a clinical trial. In the trial, patients with IPF who received Actimmune® did no better than patients who received placebo. If approved, pirfenidone (expected in 2010) will be the first drug approved for treatment of IPF. It is likely to be a high-cost specialty drug.
• HEREDITARY ANGIOEDEMA (HAE)

In 2008, Cinryze™ (C1 esterase inhibitor) became the first drug approved for hereditary angioedema, a rare genetic disorder characterized by recurrent, unprovoked episodes of severe edema involving the face, larynx, extremities, and gut. Cinryze was approved for prevention of HAE episodes but is also in development for treatment of acute attacks.

Two other drugs for acute HAE episodes may also reach the market in 2009. Ecallantide blocks kallikrein, an inflammatory mediator, and Berinert is a C1 esterase inhibitor similar to Cinryze. Although utilization of these agents is likely to be small because HAE is rare, coverage of these new drugs under the pharmacy benefit is likely to contribute to unit-cost growth in this category.

Finally, icatibant, a bradykinin antagonist, is also in clinical development for this disorder. Bradykinin is believed to be one of the major mediators of the edema seen with this condition.

Examples of ambulatory-use respiratory drugs in the pipeline are listed in Table 13.

<table>
<thead>
<tr>
<th>Year</th>
<th>Generic name</th>
<th>Uses</th>
<th>Potential impact on drug trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>indacaterol</td>
<td>Asthma, chronic obstructive pulmonary disease</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>treprostinil (inhaled)</td>
<td>Pulmonary arterial hypertension</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>tadalafil</td>
<td>Pulmonary arterial hypertension</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ecallantide</td>
<td>Hereditary angioedema</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>Berinert®</td>
<td>Hereditary angioedema</td>
<td>$$</td>
</tr>
<tr>
<td>2010</td>
<td>aztreonam inhalation</td>
<td>Cystic fibrosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>aclidinium</td>
<td>Chronic obstructive pulmonary disease</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>fluticasone + formoterol</td>
<td>Asthma</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>mometasone + formoterol</td>
<td>Asthma</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>roflumilast</td>
<td>Asthma, chronic obstructive pulmonary disease</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>tobramycin inhalation powder</td>
<td>Cystic fibrosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>pirfenidone</td>
<td>Idiopathic pulmonary fibrosis</td>
<td>$$</td>
</tr>
<tr>
<td>2011</td>
<td>denufosol inhalation</td>
<td>Cystic fibrosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>mannitol inhalation</td>
<td>Cystic fibrosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>icatibant</td>
<td>Hereditary angioedema</td>
<td>$$</td>
</tr>
</tbody>
</table>

$ = potential to cause a <2% increase in this category’s trend.
$$ = potential to cause a >2% increase in this category’s trend.
Bold text indicates potential specialty drugs.
Oncology agents

Contribution to plan spending (2008): 3%
Projected contribution to trend (2009 to 2011): 5%

Projected trend

Table 14. Drug trend projection for oncology agents*

<table>
<thead>
<tr>
<th>Year</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utilization increase</td>
<td>1% to 2%</td>
<td>2% to 3%</td>
<td>2% to 3%</td>
</tr>
<tr>
<td>Price and mix increase</td>
<td>11% to 12%</td>
<td>10% to 11%</td>
<td>9% to 10%</td>
</tr>
<tr>
<td>Annual total</td>
<td>12% to 14%</td>
<td>12% to 14%</td>
<td>11% to 13%</td>
</tr>
</tbody>
</table>

*TProject change in drug spending on a plan ingredient cost PMPY basis

TREND PREDICTIONS

Key developments that are likely to shape drug trend in the oncology category over the next 3 years:
- An increase in the number of patients receiving long-term treatment with more targeted oral oncology drugs
- Continued growth in the use of combination treatments for various types of cancers
- New oral oncology drugs and expanding indications for existing drugs for the treatment of various cancers
- Injectable monoclonal antibodies to treat various cancers

Trend driver: Oral kinase inhibitors such as Gleevec®, Sutent®, Nexavar®, Tykerb®, Tarceva®, and Tasigna®
Trend moderator: Several first-time generic oncology agents, including Femara® (letrozole), Arimidex®, Casodex® (bicalutamide), and Temodar® (temozolomide)

The quest to find a cure for cancer continues, and scientists are starting to better understand how targeted drug therapies and improved biomarker and genetic testing can transform cancer treatment. The FDA recently appointed a new chief scientist to be involved in the field of genomics, and a recent FDA Oncology Advisory Committee discussed clinical trial design for validating biomarkers and selecting patients for drug use based on this information. Eventually the results of these genetic and biomarker tests may be included in the package inserts of various drugs, in an effort to improve outcomes, minimize toxicity, and identify which patients will respond to certain treatments. As a result, cancer therapy may become the leader in the field of personalized medicine.

In addition, almost 750 new cancer drugs and new indications for existing cancer drugs are in clinical development. Thus, plan costs for oncology drugs, especially the more targeted and long-term oral drugs, will continue to grow briskly in utilization and cost over the next 3 years.

CANCER TREATMENT

Treatment trends
Injectable cytotoxic chemotherapeutic drugs such as doxorubicin are often used for many types of cancers; these agents need to be administered in a physician’s office, clinic, or hospital by intravenous infusion and are given in short cycles because of their severe side effects. On the other hand, the availability of new, more targeted, and better tolerated cancer drugs is causing a paradigm shift to long-term maintenance use of these therapies for many types of cancer. Regrettably, these treatments are expensive; their use long-term and in combination regimens frequently exceed $5,000 to $10,000 for a month of therapy. Many new cancer drugs are incremental to current treatments, and as a result, they may be significant drivers of utilization growth.
Fortunately, the incremental costs of the new cancer treatments may be paying off. According to a National Cancer Institute report, the incidence of and death rates for all cancers have decreased as patients benefit from early detection, a decline in smoking, and better treatment options.73

**New, more targeted drugs**

Novel oral and injectable cancer drugs will continue to be important trend drivers over the next few years because of the large number of recently approved drugs, the large number of oral drugs in the pipeline, and the likelihood of expanded indications and off-label usage for these products. New targeted cancer treatments in the pipeline include multikinase inhibitors, oral vascular endothelial growth factor (VEGF) inhibitors, and injectable monoclonal antibodies.

**Multikinase inhibitors**

Multikinase inhibitors are oral small molecules designed to inhibit the growth and development of tumor cells by targeting various kinase-signaling enzymes at different sites of tumor development. Gleevec was the first multikinase inhibitor approved by the FDA for the treatment of Philadelphia chromosome—positive chronic myeloid leukemia (CML). Gleevec dramatically improved patient survival and changed the way CML was treated, turning an acute and often fatal illness into a chronic condition that can be managed with long-term oral therapy. Gleevec is also approved for the treatment of gastrointestinal stromal tumor (GIST).

Recently, a large number of multikinase inhibitors were approved by the FDA, including Nexavar, Sutent, Sprycel®, Tykerb, and Tasigna. Nexavar is approved for the treatment of advanced renal cell and liver cancer, Sutent is approved for advanced renal cell cancer and Gleevec failures with GIST, Tykerb is approved for advanced or metastatic breast cancer, and Sprycel and Tasigna are both approved for Gleevec-resistant GIST. These drugs are also under clinical development for the treatment of various other cancers (e.g., lung, breast, pancreatic, and skin cancers). Some of these drugs may soon receive additional FDA indications, further contributing to utilization and unit-cost growth in this category. Finally, several oral multikinase inhibitors are in late-stage clinical development and may receive approval by the FDA over the next several years; they include vandetanib for the treatment of lung cancer and motesanib for lung and breast cancer.

**Vascular endothelial growth factor (VEGF) inhibitors**

VEGF inhibitors are designed to starve the cancer cells of oxygen and food, thus inhibiting the growth and development of tumor blood vessels. The VEGF inhibitor bevacizumab (Avastin®) is an injectable monoclonal antibody that is FDA approved for the treatment of advanced colorectal and metastatic lung cancer and for metastatic human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer. Avastin is also under clinical development for other cancers and has several supplemental BLAs pending approval, including the treatment of first-line metastatic renal cell carcinoma and glioblastoma (an aggressive type of brain cancer). These additional indications could be approved by the FDA during the second half of 2009. Another VEGF inhibitor under clinical development, pazopanib, is an oral, once-daily drug for the treatment of breast cancer, renal cell cancer, and sarcomas. It could become the first FDA-approved oral VEGF inhibitor.

**Monoclonal antibodies**

Monoclonal antibodies are protein-based injectable drugs that usually target and attach to specific parts of cancer cells, thereby helping the body’s own immune system attack and kill or inhibit the growth of the tumor. Rituxan was one of the first monoclonal antibodies developed for the treatment of non-Hodgkin’s lymphoma. Other monoclonal antibodies approved for the treatment of various cancers include Herceptin® for breast cancer, Erbitux for colon and head and neck cancer, Vectibix for colon cancer, and Mylotarg® for acute myelogenous leukemia. These agents are often given in combination with traditional chemotherapy to achieve the greatest benefit. All these agents are under clinical development for the treatment of various other cancers, including Vectibix for head and neck cancer and Erbitux for pancreatic and lung cancer. As a result, some of these drugs may receive additional FDA indications over the next several years. In addition, several other monoclonal antibodies are under clinical development, including ipilimumab for metastatic melanoma and ofatumumab for chronic lymphocytic leukemia.
The number of new oncology drug approvals may decline in 2009, but this lull will be short-lived as there are many agents in late stage clinical development and several of these agents could receive approval in 2010 or 2011. The most prominent introductions of orally administered drugs include Zactima® for lung and breast cancer, axitinib for thyroid cancer, alvocidib for chronic lymphocytic leukemia, motesanib for breast and thyroid cancer, lonafarnib (Sarasar®) for breast cancer and myelodysplastic syndromes, and pazopanib for breast cancer, renal cell cancer, and sarcomas (Table 15).

**SUPPORTIVE CARE**

Supportive care therapies represent a considerable share of the drug costs for cancer treatment. The growth rate in the use of drugs to treat neutropenia is expected to sustain its momentum over the next 3 years, and the continuing shift from Neupogen® (filgrastim) to Neulasta® (pegfilgrastim) is likely to increase unit costs for these treatments.

A potential new drug called L-glutamine (Saforis®) received an FDA approvable letter for the treatment of chemotherapy-induced mucositis (painful mouth sores). However, the FDA has requested an additional clinical trial; if it is positive, this could become the first FDA-approved drug to treat one of the complications associated with chemotherapy.

Two new drugs were approved by the FDA toward the end of 2008, romiplostim (Nplate®) and eltrombopag (Promacta®) for the treatment of idiopathic thrombocytopenic purpura or low platelet counts. Both of these medications are also under clinical development for chemotherapy-induced thrombocytopenia. If the clinical data are positive, this will significantly drive utilization of these drugs because options to treat this chemotherapy-associated disorder are limited.

**First-time generics**

Several first-time generics for oncology drugs may be approved, including Femara (letrozole) and Arimidex (anastrozole) for breast cancer, Casodex (bicalutamide) for prostate cancer, and Temodar (temozolomide) for brain and skin cancer. However, the cost and utilization of these generic drugs will eliminate any potential savings.

Examples of ambulatory-use oncology drugs in the pipeline are listed in Table 15.

Table 15. Some ambulatory-use oncology agents in the pipeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Generic name</th>
<th>Uses</th>
<th>Potential impact on drug trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>vandetanib</td>
<td>Non-small cell lung, breast cancer, and thyroid cancer</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ipilimumab</td>
<td>Metastatic melanoma</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ofatumumab</td>
<td>Chronic lymphocytic leukemia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>lonafarnib (Sarasar®)</td>
<td>Breast cancer and myelodysplastic syndromes</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>L-glutamine suspension (Saforis®)</td>
<td>Chemotherapy-induced mucositis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>sipuleucel-T (Provenge®)</td>
<td>Prostate cancer vaccine</td>
<td>$</td>
</tr>
<tr>
<td>2011</td>
<td>panobinostat</td>
<td>Chronic myeloid leukemia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>axitinib</td>
<td>Thyroid cancer</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>alvocidib</td>
<td>Chronic lymphocytic leukemia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>eribulin</td>
<td>Breast cancer</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>pazopanib</td>
<td>Sarcoma</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>motesanib</td>
<td>Breast cancer and thyroid cancer</td>
<td>$</td>
</tr>
</tbody>
</table>

$ = potential to cause a <2% increase in this category's trend.
$ = potential to cause a >2% increase in this category's trend.

Bold text indicates potential specialty drugs.
Other therapeutic agents

Pipeline developments in several other therapeutic categories may also have a significant influence on drug cost trend over the next 3 years (Table 16). These include new drug treatments for bacterial and viral infections (including HIV), male and female sexual dysfunction, dermatologic diseases such as psoriasis, gastrointestinal disorders such as gastroesophageal reflux disease (GERD), and several orphan conditions such as cryopyrin-associated periodic syndrome.

Table 16. Other therapeutic categories: Some ambulatory-use drugs in the pipeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Generic name</th>
<th>Uses</th>
<th>Potential impact on drug trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>motavizumab</td>
<td>Prophylaxis of respiratory syncytial virus infections</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ustekinumab</td>
<td>Chronic plaque psoriasis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>latanoprost + timolol</td>
<td>Glaucoma</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>bepotastine</td>
<td>Allergic conjunctivitis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>crofelemer</td>
<td>Irritable bowel syndrome</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>clostridial collegenase</td>
<td>Dupuytren's contracture</td>
<td>$$</td>
</tr>
<tr>
<td>2010</td>
<td>TMC-278</td>
<td>HIV/AIDS</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>vicriviroc</td>
<td>HIV/AIDS</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>boceprevir</td>
<td>Hepatitis C</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>dutasteride + tamsulosin</td>
<td>Benign prostatic hypertrophy</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>dexamethasone intravitreal injection</td>
<td>Diabetic macular edema</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>diquafosol</td>
<td>Dry eyes</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>alprostadil topical gel</td>
<td>Erectile dysfunction</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>mepolizumab</td>
<td>Hypereosinophilic syndrome</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>tifacogin</td>
<td>Community-acquired pneumonia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>casopitant</td>
<td>Chemotherapy-induced nausea &amp; vomiting</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>canakinumab</td>
<td>Cryopyrin-Associated Periodic Syndromes</td>
<td>$</td>
</tr>
<tr>
<td>2011</td>
<td>elvitegravir</td>
<td>HIV/AIDS</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>telaprevir</td>
<td>Hepatitis C</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>clevudine</td>
<td>Hepatitis B</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>esmirtazapine</td>
<td>Postmenopausal symptoms</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>corifollitropin</td>
<td>Infertility</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>testosterone gel</td>
<td>Hypoactive sexual desire disorder</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>afibercept</td>
<td>Age-related macular degeneration</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>rebamipide</td>
<td>Dry eyes</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>AZD3355</td>
<td>Gastroesophageal reflux disease</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ABT-874</td>
<td>Chronic plaque psoriasis</td>
<td>$</td>
</tr>
</tbody>
</table>

$ = potential to cause a <2% increase in this category’s trend.
$$ = potential to cause a ≥2% increase in this category’s trend.
Bold text indicates potential specialty drugs.
SETTING THE STAGE FOR REFORM

PHARMACY AT THE FOREFRONT
Now is the time for healthcare reform. Why reform and why now? Our system is fragmented, inefficient, and often ineffective. Our current cost of care is unsustainably high and out of sync with the quality of care.

In the United States (U.S.), there are as many as 47 million people who have no healthcare coverage, or are underinsured.\(^3\) In the current economic climate; even more Americans are likely to lose access to adequate care. It is universally recognized by policymakers, healthcare providers, payers, and the American people that change is needed. Those involved in the delivery of healthcare have an opportunity—and a responsibility—to offer leadership and real solutions to improve clinical outcomes in a more efficient and cost-effective manner.

### Challenges in the current system

#### A Disparity Between the Cost of Healthcare and Clinical Outcomes

Healthcare spending has consistently accelerated over the past several decades, reaching unsustainable levels. In the U.S., national healthcare spending is expected to increase from $2.2 trillion in 2007 to $2.4 trillion in 2008 and will continue to rise to $4.4 trillion by 2018.\(^4\) The per capita spending on healthcare—more than $7400 per person per year—is at least twice that of most other developed countries.\(^5\) In fact, out of 30 countries ranked, the U.S. had by far the highest spending on healthcare per capita.\(^6\)

The current system is designed to reactively manage acute illness; in most cases, it is not set up to manage chronic conditions or proactively reward wellness—the equivalent of deciding not to pay $30 to change a car’s motor oil but instead pay thousands of dollars to replace the motor when it fails. This short-term orientation obviously results in more costly and intensive services. Additionally, the practice of “defensive medicine” in response to the potential for malpractice litigation adds an estimated $200 billion to the yearly tab for American healthcare.\(^7\) These are but some of the factors responsible for what has been termed, “the perfect storm of overutilization,” which occurs across a broad array of service providers and supporters.\(^8\)

What value is gained from this hyper-inflated spending? In short—none. There is no appreciable difference in perceived quality or access.\(^9\) For example, the life expectancy and mortality rates for the U.S. fall short of many other developed countries that spend significantly less per capita.\(^5\) The U.S. is ranked 22nd out of 30 countries in life expectancy; U.S. life expectancy is below the average of 78.3 years. Mortality rates are also higher for the U.S. than many countries at 6.1 deaths per 1,000 people compared with the average rate of 5.9 deaths per 1,000 people reported across 30 developed countries. Years of life lost from natural causes is much greater in the U.S. compared with countries such as Japan, Iceland, Sweden, Australia, and Canada, where per capita healthcare spending is roughly half that of the U.S.\(^6\)
Recent information from the Dartmouth Atlas Project highlights the disconnect between higher healthcare spending and better clinical outcomes in patients with chronic diseases. Many patients with chronic disease are treated by multiple physicians, who may not routinely coordinate their services. As a chronic disease progresses, the level of care delivered increases significantly, along with the associated costs. Often treatment is either redundant or conflicting, creating even more clinical issues that further complicate the level of care and treatment.

Approximately 32% of total Medicare spending occurs during the last 2 years of life for a patient with a chronic disease, with much of it paid to physicians and hospitals (Medicare Part A and Part B) associated with repeated hospitalizations for treatment that does not appreciably alter the inevitable outcome, and often adds to the suffering of the patient and anguish of their families. Some of this expense could be averted with a more connected and integrated system.

“This report [Dartmouth Atlas Project] should end the ‘more is better’ myth in healthcare.”
—Donald Berwick, M.D., M.P.P. (Institute for Health Care Improvement)

Not only are costs and value for the healthcare delivered out of sync, but, according to findings of a recent study, our healthcare system wastes more than 30% of the total healthcare dollars that are spent. The study noted the following areas as examples of the sources of the wastage: excess use of some diagnostic and treatment procedures, overuse of emergency care facilities, and misuse and/or underuse of medications. Steps put in place to eliminate waste could provide an estimated $700 billion opportunity to improve the way we administer, manage, and deliver healthcare.

THE LACK OF REAL-TIME AND ACCURATE HEALTHCARE INFORMATION

Our healthcare system comprises 1 million hospital beds, 850,000 physicians, millions of allied health professionals, and about 1,000 health insurance companies. In the U.S., pharmacies dispensed 3.8 billion prescriptions in 2008. Under optimal circumstances, communication and data-sharing across all providers of care should be instantaneous and seamless, enabling better decisions, ubiquitous measurement, transparency, and accountability.

That would be possible if healthcare were “wired.” Today’s reality, however, is very different. Each portion of the system operates independently and real-time communication rarely occurs. Often there is a complete lack of information sharing, which impedes informed decision-making. This negatively impacts the quality of care as well as overall costs. The significant inefficiencies in the healthcare system are exemplified by duplicated tests and procedures, as well as the likelihood of misdiagnoses due to the lack of complete information.

Tragically, this lack of connectivity also results in medical errors, which over a 3-year period, averaged 195,000 deaths annually. One review of 41 million Medicare patients’ medical records from 2004 to 2006 identified $8.8 billion in error-associated costs and 238,837 potentially preventable deaths. Compared with 25 other developed countries, the U.S. has the third-highest mortality related to medical errors.

Another outcome of the unwired environment is medication errors. An estimated 1.5 million preventable serious medication errors occur each year in the U.S., which translates into $177 billion spent annually on the associated costs of morbidity and mortality. This means we spend nearly as much repairing the damage caused by drug-related morbidity as we spend on the drugs in the first place. (National U.S. spending in 2006 was $217 billion.)
THE BURDEN OF CHRONIC AND COMPLEX DISEASE

“Chronic disease is the No. 1 cause of death and disability in the U.S., and patients with chronic diseases account for 75% of the nation’s health care spending.”
—Partnership to Fight Chronic Disease

Half of all Americans are under treatment for at least one chronic disease. For patients initially diagnosed with chronic or complex conditions, drugs are the first choice for medical intervention 88% (131 out of 149) of the time. Care of patients with chronic and complex diseases accounts for 75% of medical costs and 96% of total drug spending in the U.S. However, about half of all patients abandon their prescribed therapy in the first year of treatment. Indirect costs linked to absenteeism, short- and long-term disability, and presenteeism (i.e., present at work but less than fully productive) can exceed associated direct healthcare costs by two to three times—making even more critical the rigorous management of these patients and tighter adherence to ongoing care.

Major contributors to these numbers include the epidemic of obesity, the persistence of tobacco and substance abuse, and physical inactivity. As the average age of our population rises, without a paradigm shift that changes the status quo, it is expected that the number of individuals with chronic disease will similarly increase (Figure 1).

Figure 1. Expected growth in chronic disease in 20-year period (2003-2023)
Source: DeVol R, et al.

The systematic adoption of protocol-driven, evidence-based healthcare is necessary to improve effectiveness and efficiency—enhancing outcomes and reducing costs. In today’s healthcare environment, patient care data are generally maintained in paper files at the site where care is provided. If the patient moves to another site, uses multiple doctors, or is admitted to the hospital, comprehensive information is not likely to be available. Paper records are not easily portable and rarely shared as a matter of practice. Often data must be recreated at the new site of care, introducing additional costs stemming from repeated or unnecessary procedures and creating errors due to missing information.

At an emergency room, where histories are urgently needed, physicians must often make treatment decisions with virtually no information—particularly when the patient is unresponsive. In an era where we are surrounded by technology that improves our productivity, enhances our convenience, and can lower costs in virtually every aspect of our lives, it is unacceptable that healthcare remains in the technological Dark Ages.
Wiring the healthcare system

“The U.S. healthcare marketplace’s continuing failure to adopt information technology (IT) is the result of economic problems unique to healthcare, business strategy problems typical of fragmented industries, and technology standardization problems....”

—J.D. Kleinke, executive director, Omnidex Institute

Care that is delivered in a wired environment enables:

- Evidence-based protocol-driven decision making
- Access to complete diagnostic, laboratory, health, and treatment records
- Real-time data collection for measuring every aspect of care, and evaluating and improving current practices and patient outcomes
- A standardized rewards system based on the contributions that add value to the system

Where health information technology (HIT) has been adopted to date, much of the innovation has taken place in silos, without consideration for interoperability and in the absence of government standards. Available products with proprietary systems can’t “talk” with other systems and have been burdened by reliability issues, discouraging the early adopters who have realized minimal return for their capital investment.

Strong policy leadership will be needed to solidify the necessary foundation to ensure the success and widespread adoption of wired healthcare in America. We first must develop an operating framework, create universal standards, build a trusted repository for sensitive information, and ensure privacy. The government has recently stepped in to assist the private sector. The American Recovery and Reinvestment Act of 2009, signed into law by President Obama, includes $2 billion in funds for grants and loans from the Office of the National Coordinator for Health Information Technology to facilitate the adoption of HIT. An additional $17.2 billion is set aside for Medicare and Medicaid to reward hospitals and physicians with financial incentives for using electronic systems.

Recent data suggest that although some physicians have adopted e-prescribing, they remain in the vast minority. A 2008 survey conducted by the National Center for Health Statistics, found that approximately 40% of reporting physicians indicated that they used full or at least partial electronic medical record technology; one-fifth reported using a minimally functional system. That was just marginally better than the results from the identical survey conducted in 2006. Meanwhile, figures are even lower for fully integrated medical records, suggesting that only 4% of practicing physicians use such technology. This low acceptance rate was confirmed in a 2009 hospital survey, which found adoption of electronic systems ranging from 1.5% for a fully integrated system to 7.6% for a basic system, despite agreement that HIT can lead to improved care and outcomes.

A study of 72 urban hospitals evaluated the effect of automation on clinical and financial outcomes of approximately 167,000 patients with myocardial infarction, heart failure, coronary artery bypass, or pneumonia. Increased use of HIT was associated with a 16% reduction in complications. Automation of test results, order entry, and decision support were associated with lower costs for hospital admissions, and overall cost savings reached $54 million for just 72 hospitals.

Not all electronic health records are created equal. Some systems include computerized decision-support (CDS) tools—these are evidence-based protocols, such as treatment algorithms and a review for potential drug interactions that are designed to enhance safety and improve care. CDS may also provide a pathway to remind clinicians about the details of a protocol, helping to keep the evidence-based guidelines for a specific condition readily available. Application of electronic systems to help ensure that protocols are available and followed is a key component of the needed healthcare reform,
especially in the case of patients with chronic and complex conditions. One study, which included more than 2,000 adults with high blood pressure, assessed the benefits of computerized health records with and without CDS. It showed that physicians with access to CDS increased recommended medication prescribing compared to physicians who didn’t have the benefit of CDS.26

In addition to providing better clinical outcomes, increasing adherence to evidence-based national prescribing guidelines and use of electronic medical records can also provide cost savings. One study estimated that over a 15-year period the savings from using electronic medical records in the hospital setting could exceed $370 billion; in the ambulatory setting the forecasted benefit was similarly impressive at $142 billion.27

Kaiser Permanente recently reported on a pilot program using a comprehensive electronic health records (EHR) system in one of its care regions.28 They observed a significant decrease (26%) in office visits, accompanied by a nearly nine-fold increase in the number of scheduled telephone visits. While a small increase (5%) in the number of emergency department visits was observed during the same period, it did not account for the total decrease in office visits. Patient Healthcare Effectiveness Data and Information Set (HEDIS®) scores from 2004 (pre EHR) and 2007 (post EHR) collected during the study showed that the level of patient satisfaction with their healthcare was maintained. Overall, the results of the pilot program reported by Kaiser Permanente strongly suggest that an integrated and comprehensive EHR can shift the pattern of ambulatory care toward more-efficient contacts for patients and providers, while at a minimum maintaining quality of care and patient satisfaction.

Using the power of technology to create a ubiquitous source of health information is being pursued in other countries as well. In Germany, for instance, efforts are underway to create an electronic health card that each citizen would carry in his or her wallet.29 The goals for this initiative include improving communication between practitioners throughout the healthcare system and decreasing the risks of drug interactions and contraindicated therapies. It is envisioned that this card will contain information including insurance eligibility and other administrative data along with drug history, hospital discharge summaries, and a complete electronic health record.

## PROTOCOL-DRIVEN HEALTHCARE

“The key to prevention [of errors] lies within other industry standards, in which safety measures have shown decreases in errors.”
—Theresa M. Pape26

Imagine boarding a plane. You take it for granted that processes and protocols, developed from evidence-based research, assist the crew during pre-flight safety checks. Those checklists also guide decisions should any emergency arise. In January 2009, the skill and experience of the pilot and crew, combined with the flawless execution of these protocols, enabled a crippled jet to safely land in the Hudson River. All passengers and crew aboard were rescued.

In healthcare, a protocol is a recommended course of action based on an assessment of scientific evidence or accepted standards of care. While other high-risk organizations, such as the aviation industry, have developed protocols to improve quality and minimize errors within their organizations, healthcare has been reluctant to embrace this concept—largely due to concerns about interfering with professional judgment in the practice of medicine.

Healthcare protocols are designed to complement the experience of a physician. Developed by medical researchers and experts in professional medical organizations, these evidence-based protocols are formulated from study results and medical practice findings. In today’s environment, the rate of scientific discovery challenges an individual physician’s ability to keep pace. Wiring the system and adhering to protocols have proven to be effective tools to ensure consistency
in care and improve patient outcomes. Adherence to standardized protocols has an additional benefit in that they could be used to provide physicians with a shield against frivolous lawsuits and avert the need to practice defensive medicine—which, as part of a plan to reform the tort system, could reduce healthcare spending by as much as $200 billion a year.7

Beyond improving care and reducing costs, protocols provide structure and improve patient safety by decreasing variation.30 Safety in clinical practice is based on a combination of a structure that reduces the possibility of harm and evidence that increases the likelihood of an action resulting in a favorable outcome. The expected decrease in variation and increase in compliance associated with evidence-based protocols should decrease the error rate and enhance patient safety.

Employing protocol-driven healthcare provides an objective measure that may be applied to help clarify decisions of liability. Physicians prudently following protocols should be shielded from litigation that is aimed at pointing blame for unavoidable negative health outcomes. The National Coalition on Business and Health supports the incorporation of evidence-based practice guidelines as a means to control health and medical malpractice insurance costs and simplify the tort process.32

Protocols can vary from a simple checklist to a much more detailed and structured plan.

A recently published multicenter, multinational study highlights the impact of a basic tool on quality and outcomes of care. Use of a simple 19-item surgical safety checklist in a socioeconomically diverse population of patients 16 years of age or older undergoing surgery resulted in a 36% reduction in the rate of complications.33 The in-hospital death rate was reduced by 47%, from 1.5% to 0.8%.

Utilizing standardized protocols in pharmacy can also have a positive impact on clinical outcomes and the costs of care.

Patients seen by pharmacists working under a defined protocol that included evidence-based management guidelines for cholesterol, blood pressure, and diabetes management reduced their hemoglobin A1c measurements, an indicator of improved diabetes control. In addition, average costs for inpatient and emergency department visits dropped by $1,800 following the introduction of disciplined pharmacist management.34

Protocols enable standardization and performance-based accountability to improve outcomes. Intertwining evidence-based medicine, protocol development, and continuous quality improvement processes will improve our healthcare system.

For a patient in the midst of a heart attack, the time that elapses from arriving at the hospital for treatment to surgery (often referred to as “door-to-balloon” time) is critical. American Heart Association guidelines are based on research that linked timely heart reperfusion with better outcomes. The longer the time to reestablishing blood flow to the heart muscle, the higher the risk of disability or death.35 A door-to-balloon time of 90 minutes or less increases survival for these patients. A survey of acute care hospitals revealed door-to-balloon times that, on average, exceeded 90 minutes—even years after the 90-minute standard had been published.36 One hospital measured its door-to-balloon time to be more than 100 minutes. It then devised and put in place a standardized process for managing these heart attack patients. Using a protocol to drive care steps, within a 12-month period they improved door-to-balloon times to an average of 72 minutes.37

Coupling decision-support tools (protocols) with electronic health records can provide a foundation for quality improvement.
Physicians within a large health system selected nine standards of diabetes care for an improvement initiative. They received a baseline assessment of their patients’ adherence to these standards and a comparison with national benchmarks, as well as benchmarks across their own organization. At monthly intervals, over the following year, physicians received updates. The outcome demonstrated the benefits of standardized management for patients with diabetes—all parameters assessed either improved or stayed the same; no measures worsened. By monitoring progress, they achieved significant improvements in blood pressure and hemoglobin A1c (measures diabetes control) as well as improvement in pneumonia vaccine; flu vaccine; nonsmoking; trace protein in urine; and low-density lipoprotein (measures cholesterol). No change was noted in hemoglobin A1c less than 7 (stringent measure of diabetes control) and low-density lipoprotein less than 100 (stringent measure of cholesterol).

MODELING THE BENEFITS OF WIRED PROTOCOLS—PHARMACY AND DUR

Drug utilization review (DUR), the process of screening prescriptions for potential drug-related problems, marked the initial movement toward protocol-driven care in the practice of pharmacy, and it has been a part of pharmacy practice for more than 25 years. Its use and the sophistication of the process have evolved with time and technology (Figure 2). DUR is now considered a standard of care for the practice of pharmacy in the United States and provides an excellent example of how protocol-driven practice complements professional judgment.

Figure 2. DUR timeline

<table>
<thead>
<tr>
<th>1970s</th>
<th>1980s</th>
<th>1990s</th>
<th>2000s</th>
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<tbody>
<tr>
<td><strong>Academic roots in the U.S.</strong></td>
<td></td>
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<tr>
<td>• Don Brodie published a seminal paper on drug utilization review</td>
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<tr>
<td>• Emergence of “clinical pharmacy” practice</td>
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<tr>
<td><strong>Business applications (early 1980s)</strong></td>
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<tr>
<td>• IBM PC introduced in 1981</td>
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<tr>
<td>• Pharmacies computerized rapidly as prices declined</td>
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<td></td>
</tr>
<tr>
<td>• Computerized DUR was common in 56,000 pharmacies and hospitals</td>
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<tr>
<td>• Automated Rx billing introduced nationwide in 1987</td>
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<tr>
<td>• PBMs incorporated DUR into the Rx billing process for health plans</td>
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<tr>
<td><strong>DUR as a national mandate</strong></td>
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<tr>
<td>• 1990: Concurrent DUR mandated for Medicaid</td>
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<td></td>
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<tr>
<td>• 2004: Medication Therapy Management mandated by Medicare</td>
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The DUR process is universally applied to prescriptions regardless of how they reach the pharmacy (mail, in-person, fax, electronic). The electronic screening automatically alerts the pharmacist to a potential issue. This gives the pharmacist an opportunity to validate the prescription—determining whether the prescription should be filled or if changes are necessary. Through DUR, and in collaboration with prescribers, pharmacists improve drug therapy and prevent unnecessary or inappropriate medication use.

Medco uses an advanced DUR system with additional safety provisions that are optimized for seniors. Medco conducted a study among seniors to determine if the DUR alerts combined with pharmacist-initiated provider contact improved medication use. During the 12-month study period approximately 43,000 safety alerts were triggered, and in 56% of those cases, prescribing physicians were contacted by a pharmacist specializing in geriatrics care. The intervention resulted in a 24% rate of change—much higher than the expected 2% DUR change rate that had been reported in the literature. This landmark study demonstrated that DUR, as part of a wired environment, enables a level of pharmacy care management that improves clinical quality and enhances patient safety.
Improving healthcare: Leveraging the pharmacy model

“Effective ways to help people follow medical treatments could have larger effects on health than any treatment itself.”
—Cochrane Database Review

Addressing identified clinical gaps is an essential component of improving care. Clinical gaps in care include:
- Errors of omission (drugs not prescribed that should have been)
- Nonadherence (patients not faithfully following the physician’s recommendations)
- Errors of commission (medication errors)

## ERRORS OF OMISSION

For most common medical conditions, existing evidence guides initial therapy choices. When a protocol-based disease management guideline outlines therapeutic choices, an error of omission occurs if a patient does not receive the recommended prescription therapy, which may include one or more medications based on the diagnosis or condition. This can result in poor medical outcomes. A “failure-to-take” example is seen in patients with diabetes who are at an increased risk of heart disease. The American Diabetes Association has recommended that aspirin therapy should be given to patients with diabetes to help reduce their risk of heart disease. Yet, up to 25% of individuals with diabetes and heart disease and 60% of individuals at high risk for heart disease have not been prescribed aspirin therapy. A “failure-to-prescribe” omission may occur if a clinician fails to recognize a pattern, or, recognizing a pattern, does not initiate any action. For instance, management guidelines for hypertension recommend a need to treat a 46-year-old patient with seated blood pressure readings of 180/115 mm Hg averaged over three separate measurements. Failure to initiate treatment could be regarded as an example of error, and could lead to a worsening of the patient’s high blood pressure.

## MEDICATION NONADHERENCE

Patients will only realize the beneficial effects of a medication when it is taken as prescribed. Nonadherence—a lapse in therapy—can contribute to poor health and ultimately increase medical costs, especially for patients with chronic illness. On average, about half of all patients abandon their recommended therapy in the first year of treatment. There are many reasons for nonadherence, which include misunderstanding instructions, expense, adverse effects, forgetfulness, and patient self-diagnosis, i.e., the patient determines unilaterally that the medication is not helping and/or is unnecessary.

“In the case of diabetes, which currently afflicts 5% of the population and whose treatment accounts for 15% of all drug spending, only 7% of diabetic patients are controlling the three primary factors that could mitigate the effects of their disease and allow them to live a healthy and productive life.”
—David B. Snow, Jr., Chairman and Chief Executive Officer, Medco Health Solutions, Inc.

The link between adherence and better clinical outcomes has been well documented—particularly in several high-risk or chronic conditions.
- Diabetes
- Congestive heart failure
- Coronary artery disease
- High cholesterol
- High blood pressure
- Human immunodeficiency virus
Figure 3 provides a representative snapshot reflecting the difference in survival rates among patients with high cholesterol. Survival in patients who were adherent to prescribed statins was approximately 20% higher than for patients who were not adherent.53

Figure 3. Survival curve for statin users
Source: Ho PM et al.53

Pharmacists can play a critical role in improving medication adherence.

The Federal Study of Adherence to Medications in the Elderly (FAME) assessed the effect of pharmacist interaction with patients on medication adherence and clinical outcomes. Pharmacists offered counseling, education, and medications packaged in blister packs that were labeled to remind patients when to take their medicines. The study examined medication adherence, and the related effects on the management of blood pressure and cholesterol, in military healthcare recipients 65 years and older who were taking at least four chronic medications.54 At the end of 6 months, adherence to prescribed medications increased by at least 90 percentage points (from 5% to 98.7%). Not surprisingly, blood pressure and cholesterol levels were lower in the adherent group.

“There is no cure for medication nonadherence—ongoing efforts are needed to keep adherence a priority for patients.”
—Cochrane Database Review53

**ERRORS OF COMMISSION**

In pharmacy care, errors can be life-threatening. The prevalence of errors dictates that we implement strategies to reduce these events in every step of the process. There are multiple opportunities for introducing errors: during the prescribing stage (e.g., wrong drug, wrong dose, allergy), dispensing (e.g., wrong drug, wrong dose, interactions, allergic reactions), administration (e.g., wrong time, wrong patient), and monitoring. Understanding the process and identifying where mistakes can occur is the first step towards addressing and preventing these errors.
One observational study assessed dispensing errors in 50 pharmacies located in six cities across the U.S. and found a dispensing-error rate of four errors per day in a pharmacy filling 250 prescriptions daily, or 1.6%.

In contrast, a study to measure the rate of dispensing errors in an automated mail-order pharmacy found a dispensing error rate of less than 1 per 1,000 (0.1%) prescriptions, clearly demonstrating the key role that automation can play in reducing dispensing errors.

One innovation that has been applied to reducing medication errors is bar coding. This technology has been employed to address medication errors in dispensing and administration. The goal of bar coding is to provide assurance that the right medication reaches the right patient. By providing a unique bar code for each medication and for the patient, a level of safety is introduced. In the hospital setting, scanning the medication package and a matching patient wristband allows the computer to confirm the right drug is going to the right patient.

Using direct observation before and after bar code implementation, data on dispensing errors and potential adverse drug reactions were collected in a large academic health center. Implementation of bar code technology led to an 85% relative reduction in dispensing errors and a 74% relative reduction in potential adverse drug reactions.

Simple implementation of technology that promotes automation and reduces the likelihood of error is an essential step to reducing medication errors and improving clinical outcomes. Technology must also be coupled with protocol-driven care and continuous improvement programs to yield measurable progress in medication safety. Moreover, fully wired systems need to facilitate the evaluation of medication error protocols as well as identify and address possible new sources of error. This continuous feedback of information on how the system is functioning will allow us to improve care and outcomes.

**BUILDING ON INNOVATION IN PHARMACY PRACTICE**

Pharmacy provides a proven example of the benefits cascading from a wired healthcare delivery system by using leading-edge technology to support protocol-driven healthcare, facilitate communication, and help improve patient outcomes. In addition, prescription data transactions are real-time, capturing clinical and financial information for each claim.

Three leading pharmacy benefit management companies—Advance PCS (subsequently acquired by CVS Caremark), Express Scripts, and Medco Health Solutions—collaborated in 2001 to form RxHub, which serves as a ubiquitous platform linking physicians and their e-prescribing devices with pharmacies and pharmacy benefit managers. At about the same time, an alliance of retail pharmacy organizations—the National Association of Chain Drug Stores (NACDS) and the National Community Pharmacists Association (NCPA)—embarked on a similar path with SureScripts.

In an unprecedented display of "coopertition"—collaboration among competitors—RxHub and SureScripts merged in 2008. This merger will provide the opportunity to leverage the strengths of each organization to improve the safety, accuracy, and efficiency of the prescribing process under a unified system. The merger combined the capabilities of RxHub’s point-of-care drug benefit information with SureScripts’ electronic prescription routing expertise. This will provide increased access to patient medication history data, offering prescribers access to expanded information to improve decision-making and support their professional judgment. More than 68 million physician-to-pharmacy electronic prescription transactions were processed in 2008. The system also fulfilled an additional 78 million requests for patient benefit information and 16 million patient drug histories. These still account for only a small percentage of all prescriptions filled, underscoring the tremendous upside potential of e-prescribing technology.

“In an era when preschoolers use the Internet to chat with friends half a world away, it is inexcusable that doctors write paper prescriptions—in Latin—which patients need to take to another professional in a process fraught with countless opportunities for error.”

—David B. Snow, Jr, Chairman and Chief Executive Officer, Medco Health Solutions, Inc.
Wired systems that support e-prescribing efficiently transfer prescription information, improve formulary compliance, and reduce errors associated with interpretation of prescriber handwriting by the pharmacist. They provide decision-support tools to prescribers that are designed to improve evidence-based drug selection and streamline processes; notify physicians of potential drug interactions, drug allergies, formulary status issues, generic availability, and dosing; and advise on whether or not a prescription has been filled.

Through data that are readily available in electronic systems, Medco is able to continuously analyze its services and update its offerings to optimize benefits for patients and plans. With a focus on promoting excellence across operations, Medco employs Six Sigma methodology to measure every aspect of its performance. By automating pharmacies for efficiency and providing pharmacists with real-time information to enhance effectiveness—and wiring every aspect of operations to coordinate care and advocate for members—Medco is able to offer its clients:

- Transparency—the ability to document clinical performance metrics by condition, document effectiveness in closing clinical gaps, and compare performance against retail pharmacies
- Accountability—the ability to deliver auditable findings for clinical services
- Improved outcomes—the ability to close gaps in care, with the potential to improve clinical and financial outcomes for members and clients

In 2009, Medicare will begin to pay physicians a 2% incentive for submitting Part B prescriptions electronically. This incentive will continue in 2010 and then decrease to 1% in 2011 and 2012, with a final incentive (0.5%) in 2013. Medicare will then begin to penalize prescribers by reducing reimbursements for those who fail to adopt e-prescribing by 2012. Private-sector health insurance plans are also adopting a similar approach for their non-Medicare beneficiaries. The combined incentives may help physicians offset the cost of purchasing e-prescribing software and speed adoption.

The savings opportunities are significant and include increased generic and formulary compliance, improved administrative efficiency, reduction in waste, and avoided hospitalizations in addition to improved clinical outcomes.

A recent study on the use of e-prescribing with formulary decision support for patients insured by two Massachusetts providers demonstrated this savings. Analyses of claims data showed a 3.3% increase in Tier 1 medication use (predominantly generic medications). For every 100,000 insured patients filling prescriptions, an estimated annual savings of $845,000 could be realized if e-prescribing with decision support was employed for 20% of prescriptions. This number could conceivably escalate to $4 million if e-prescribing with decision support were universally applied.

E-prescribing has been proven to decrease medication errors.

In a retrospective review of pharmacist-intercepted prescription errors in a single institution with an option to use e-prescribing, pharmacist-intercepted errors for handwritten prescriptions were more than 30% higher (7.4%) compared to e-prescriptions (4.9%). Errors that were identified by the pharmacist included dosage form, quality, dose, and drug allergy.
Incentives can increase the use of e-prescribing and streamline the care process.

The Southeast Michigan e-Prescribing Initiative (SEMI)—a collaboration of three major American automakers, their insurers, and Medco—launched a major pilot with physician incentives intended to maximize the use of e-prescribing. Interviews with physicians and staff found that e-prescribing met or exceeded the expectations for 9 of 10 individuals surveyed. The majority of respondents (70%) reported high satisfaction with their e-prescribing system. Greater safety, more reliable prescribing histories, and speed and ease of use were all cited as important demonstrated benefits. Users also reported a reduction in clarifying communications with pharmacies—a time-saver considered meaningful by 41% of respondents.

Barriers to the adoption of technology include the lack of standards and resistance to invest capital in a system that may be outdated before it is fully implemented.

Successful wiring of the system will require dedicated resources, a willingness to share and cooperate, and a common platform. The recent CMS e-prescribing mandate and financial support that has been pledged by the current administration should push information technology to a new level. Significant expenditure will be needed to provide physicians with education on the benefits of a fully wired healthcare system.

Innovation in the practice of pharmacy provides an opportunity to a broader application across the healthcare continuum. What began with building a wired system that allowed users access to essential information became the platform for new applications around accuracy, efficiency, contraindications, and pharmacological history. The success in the practice of pharmacy is a model for far-reaching healthcare reform. The opportunity is immense—rather than hypothesized, pharmacy practice provides numerous examples of validated clinical outcomes improvement.

**ADVANCING PHARMACOGENOMICS TO IMPROVE DRUG THERAPY**

In pharmacy, one size does not fit all—prescribing the same medication to two individuals for the same indication may elicit two completely different responses. An individual’s response to a medication is often influenced by his or her genetic makeup, which may affect the individual’s ability to metabolize the medicine—resulting in a potential overdose or underdose. In some cases, a person’s genetic predisposition will prevent the medicine from having any affect—or trigger an adverse reaction.

Pharmacogenomics—understanding the relationship between drug response and genetics—is the future of pharmacy. Twenty-five percent of all FDA-approved product labels now contain some type of genetic information.

This information can play a critical role in identifying patients who may or may not respond to certain drugs, and may also help in adjusting the dosage of drugs to optimize their efficacy and safety. Specific categories for use include:

- Clinical response and differentiation
- Risk identification
- Dose-selection guidance
- Duration of therapy
- Susceptibility and resistance

In most cases, a simple, low-cost test is used to determine a patient’s specific genetic predisposition. Clinical application of pharmacogenomic information may make it possible to stratify patients based on their predicted response to treatment regimes (e.g., drug selection and dose), leading the way for personalized medicine.
Pharmacogenomics information can now be used to help predict a patient’s level of sensitivity to warfarin, a commonly used blood thinner that has a narrow therapeutic range. This means that even a slight underdose can result in a risk of clotting and a slight overdose can result in internal bleeding or cause a stroke. In 2005, more than 3.8 million individuals in the United States were treated with warfarin at a cost of almost $963 million. This resulted in 43,000 emergency room visits for adverse events. Incorporating pharmacogenomics information into dosing algorithms for warfarin improves the prescriber’s ability to reach the most effective dose for a specific patient from the onset of treatment compared with a clinical algorithm or fixed dosing based on population averages.

Pharmacogenomics information has also been applied to the treatment of certain types of malignancies. Tamoxifen is used to prevent the recurrence of estrogen receptor-positive breast cancer. In order to exert its antitumor effects, tamoxifen must be metabolized by liver enzymes, which are subject to genetic variation and can be determined by a genetic test. This means the effective dose of the active ingredient, which influences the response to tamoxifen therapy, will vary from patient to patient, depending on whether she or he is a genetic high or low metabolizer. Studies have shown that women with specific genetic variants have a lower response to tamoxifen and have an increased chance of cancer recurrence unless they are provided an alternate treatment. As more data are collected, there may be continued improvement in the treatment approach as a result of genetic testing.

Evidence-based protocols for treatments with genetic components to identify the appropriate medications and dosing will be an increasingly important part of pharmacy practice moving forward. According to a Medco survey of 295 large employers (500 to 50,000+ employees), coverage for genetic testing is expected to increase from 15% to almost 40% over the next 3 to 5 years. However, there is room for improving awareness of these genetic tests among caregivers. Based on a Medco survey conducted during its recent tamoxifen study, 98% of physicians contacted said they were unaware that genomic tests were available to help guide the selection of the most effective medicine and dose.

In the future, DUR rules will also incorporate genetic information. If the entire healthcare system were wired, this information would be readily accessible to all caregivers making therapy decisions—optimizing outcomes and minimizing adverse effects. Genetic information also holds the promise of improving the trial-and-error process in place today with traditional population studies to assess the effectiveness and safety of promising drugs. The ability to identify the right cohort of patients through genetic testing to evaluate drugs in the pipeline could significantly improve the current process, which is cost-prohibitive and lengthy.

“The selection of a drug based on genomic biomarker profiles is desirable because it limits drug exposure to patients who will benefit/are most likely to benefit from drug treatment, avoids drug use in patients who will be/are likely to be harmed by drug treatment, or enhances safe use by optimizing drug dosing.”
—FDA briefing document for the December 16, 2008, meeting of its Oncologic Drugs Advisory Committee

REINVENTING PHARMACY CARE

Moving from traditional pharmacy to precision pharmacy, exemplified by the Medco Therapeutic Resource Centers®, is more than hope for the future—it’s a proven solution today. Recognizing the overwhelming impact of chronic and complex diseases on healthcare spending, Medco completely reinvented its pharmacy practice model. Chronic and complex conditions are part of everyday life for 50% of Medco’s members. These members account for approximately 96% of pharmacy costs and 75% of medical costs. Focusing on this population is the most efficient use of resources—delivering the highest clinical quality at the lowest cost.
Compared with the general population, patients with chronic and complex healthcare issues generally see more physicians who, independent from one another, write more prescriptions. In the context of a system where there is often insufficient coordination across prescribers, wide disparities in adherence and precious little time for counseling, this can lead to a significant number of clinical gaps in care—gaps that range from deviations in accepted treatment protocols and a lapse in patient compliance to opportunities for saving money from generics and mail order. Medco Therapeutic Resource Centers were developed to address these needs and issues, which focus on the care of patients with specific conditions, such as asthma, diabetes, or heart disease. These therapeutic centers are staffed by pharmacists who receive special training in these conditions, and immerse themselves in a daily practice tending to the needs of these specific patients.

The concept of the Medco Therapeutic Resource Centers pairs specialized pharmacist knowledge with available patient data by leveraging technology to apply evidence-based protocols to improve patient care. In effect, this care model represents a microcosm of key components of healthcare reform—wiring, protocols, and process improvement through feedback loops. The results demonstrate better adherence, improved care, fewer errors, and reductions in cost. The structure of each therapeutic center allows pharmacists to consult with physicians so that the appropriate therapy at the optimum dose meeting all relevant protocols is followed. The patient, physician, and pharmacist are then aligned with the same understanding of the medication therapy and treatment goals. Specialized pharmacists can have more informed and impactful discussions with patients and physicians due to their knowledge of a specific chronic or complex disease. This helps build trust and ensures that the collaborative goal—helping the patient remain adherent with the physician’s prescribed treatment regimen—is attained.

Medco has established 14 therapeutic centers staffed by pharmacists to specialize in the care and drug therapy of members under treatment for a chronic or complex disease condition:

- Diabetes
- Cardiovascular
- Pulmonary/Immunology
- Neurology/Psychiatry
- Gastroenterology
- Oncology
- Rare Diseases and Specialty Pharmacy Medications (eight separate therapeutic centers)

The concept of pharmacists specializing in the care of certain subsets of patients has similarities with physicians who specialize in the treatment of patients with chronic and complex conditions. These specialist pharmacists receive additional training. While many medical doctors practice alongside physicians with similar experience, the specialist pharmacist also practices in a unique environment. For example, specialist pharmacists in the diabetes therapeutic center gain expertise because they interact primarily with patients who have diabetes, physicians who treat diabetes, and peers who are also focused on pharmacy care for patients with diabetes. They acquire detailed knowledge about the medications used to treat the condition and the monitoring that is required to ensure desired therapeutic outcomes.

Patients with chronic conditions served by the therapeutic centers are stratified via evidence-based algorithms that identify their “dominant” condition—which defines the most appropriate treatment regimen. The system recognizes that patients frequently suffer from multiple conditions, so specialists across different therapeutic centers will collaborate to ensure holistic patient care. Since pharmacy is the most-frequently used health benefit, pharmacists may interact with patients four to five times more than the number of interactions with physicians. These pharmacists are then able to capitalize on their role as one of the most trusted professionals. Any patient, whether served via mail or at retail, can speak with a specialist pharmacist. Most patients (>86%) are agreeable to discuss their medications since they have initiated the call to address a concern. The pharmacists also make outbound calls when there is a medication safety concern.

**IDENTIFYING AND CLOSING GAPS IN CARE**

Using analytic capabilities, Medco developed the Health Action Plan to precisely identify patients who have gaps in care associated with their chronic condition. The specialist pharmacist reviews this evidence-based algorithm, which is an
electronically generated assessment that identifies gaps in care specific to that patient. The specialist pharmacist now has an opportunity for a “teachable moment.” Both patient and pharmacist are focused on addressing the patient-specific concerns and the pharmacist can provide the counseling designed to benefit the patient. By striving to close the gaps in care (e.g., the patient is not receiving a medication or is not being monitored according to standards of care) pharmacists assess and address barriers to compliance—which lead to correcting errors and connecting patients with other available resources.

Specialist pharmacists can serve as collaborators and coordinators to the treating physician by providing an additional clinical safety net for identifying gaps in care across providers. They also help patients receive the benefits of adhering to evidence-based protocols and reinforce counseling so that patients understand and follow through on the prescriber’s objective. These actions also lead to savings opportunities. With this novel approach, Medco has redefined pharmacy practice—and quality of patient health.

**Improved care for patients and better adherence**

*Medco Therapeutic Resource Centers* have demonstrated that this model is effective in closing clinical gaps in care across disease states. Diabetes—one of the most prevalent conditions in America—can be treated successfully with proper adherence. Patients under care for diabetes often have other risk factors that must be managed and coexisting diseases that must be treated. Medco’s Diabetes Therapeutic Resource Center has successfully used a protocol-driven approach combined with integrated data systems to significantly close the gaps related to ongoing care. In a recent study, gaps in care were analyzed over a 90-day period from six clients who have 600,000 members under care for conditions that include diabetes and pulmonary and cardiovascular disease. These gaps ranged from omissions of essential medications or laboratory tests to nonadherence. Medco quickly identified and closed 7% of the gaps in care related to patients undergoing treatment for diabetes who, according to national guidelines, should have been prescribed a statin as part of their treatment regimen, but were not in conformance to those evidence-based protocols. Medco also closed 24% of the gaps related to patients receiving insulin treatment for diabetes who failed to regularly monitor their blood sugar levels. Medco’s approach also successfully closed gaps in care for other chronic diseases: high blood pressure (81%), high cholesterol (74%), and asthma (15%) (Figure 4).71

**Figure 4.** The *Medco Therapeutic Resource Centers* model closes gaps in care for patients with chronic complex diseases

Source: Medco data

Note: The data include information on 600,000 patients with diabetes, pulmonary disease, and/or cardiovascular disease.
Reductions in cost
In another analysis of the 600,000-member cohort, 2 years of pharmacy and medical data were reviewed to evaluate care for patients with high blood pressure receiving care in the therapeutic centers setting vs. traditional pharmacy care. This care was associated with improved medication adherence and reduced overall costs of $700 per patient compared to traditional care. This was accomplished by improved adherence to evidence-based standards. In addition, the more patients engaged the therapeutic centers for their therapy, the better their adherence was, and the lower their overall cost of care.

Adherence to evidence-based protocols
Diabetes care was the focus of an added analysis of the 600,000 patients. Quality-of-care metrics for patients enrolled in the Diabetes Therapeutic Resource Center were compared with those patients receiving pharmacy services. Several key findings substantiated the support of specialized, focused care for these chronic disease patients (Table 1):
- Patients in the diabetes center group were more likely to be adherent to their diabetes medications (78% vs. 56.5%).
- Antihypertensive medication compliance was greater in the diabetes center patients (83% vs. 65.4%).
- Cholesterol-lowering medication adherence was greater in the therapeutic center patients (80% vs. 62.4%).
- More therapeutic center patients meeting criteria for cholesterol-lowering medication received this type of medication (76.6% vs. 63%).

Table 1. Diabetes Therapeutic Resource Center improves adherence to evidence-based protocols compared with the average of five national retail chains
Source: Medco data

<table>
<thead>
<tr>
<th>Key Diabetes Metrics</th>
<th>Medco Diabetes TRC (%)</th>
<th>Retail Chain Average (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average blood sugar</strong> (Protocol: lower to prevent amputation, blindness, kidney failure, nerve damage, heart attack, and stroke)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess average blood sugar (A1c test in past year)</td>
<td>69.2</td>
<td>64.7</td>
</tr>
<tr>
<td>Insulin users monitoring blood sugar with test strips</td>
<td>60.7</td>
<td>55.9</td>
</tr>
<tr>
<td>Adherence to diabetes medications</td>
<td>78.1</td>
<td>55.3</td>
</tr>
<tr>
<td>Prevent emergency room visits for insulin users</td>
<td>80.2</td>
<td>77.7</td>
</tr>
<tr>
<td><strong>Blood pressure</strong> (Protocol: lower to prevent heart attack, stroke, and kidney failure)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use ACE inhibitor/ARB (&gt;55)</td>
<td>77.0</td>
<td>69.1</td>
</tr>
<tr>
<td>Use ACE inhibitor/ARB (% blood pressure medication users)</td>
<td>86.8</td>
<td>83.8</td>
</tr>
<tr>
<td>Adherence to any blood pressure medication</td>
<td>83.3</td>
<td>64.2</td>
</tr>
<tr>
<td><strong>Cholesterol</strong> (Protocol: lower to prevent heart attack and stroke)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess LDL-cholesterol (obtain LDL-C test)</td>
<td>63.8</td>
<td>59.9</td>
</tr>
<tr>
<td>Use cholesterol medication</td>
<td>76.6</td>
<td>62.4</td>
</tr>
<tr>
<td>Adherence to cholesterol medication</td>
<td>80.5</td>
<td>61.2</td>
</tr>
</tbody>
</table>

Note: This table demonstrates the differences in the percentage of patients with diabetes who achieved medication adherence between Medco Therapeutic Resource Centers, which practice evidence-based protocol-driven care, and retail chain pharmacies. The metrics that were assessed are the key indicators of successful control of diabetes and the disease’s associated comorbidities. Data in the column “retail chain average” were calculated based on an average of five national retail-chain pharmacies.

Medco will continue to follow these patients to determine whether changes in adherence have been sustained.

The protocol-driven care model of the Medco Therapeutic Resource Centers is an example of a fully wired system. All prescription drug data and available complementary medical information are used to identify and close gaps in care, improve care proactively, and prevent medication issues. This real-time approach to the care of chronically ill patients is a significant step forward in improving clinical outcomes and reducing healthcare spending.
The future of healthcare

America faces monumental challenges. Despite unprecedented financial strains, our country must address the needs of large numbers of very sick people afflicted with multiple chronic diseases—whose treatment includes multiple physicians prescribing a regimen of medications.

When patients can’t afford or don’t take their medicines, or their treatment is not consistent with evidence-based protocols, tragic complications and consequences are inevitable, the costs are unsustainable, and the goal of extending care to the uninsured becomes impossible.

Medco’s pharmacy paradigm has demonstrated:
- Pharmacists with specialized training and guided by real-time data matched against evidence-based protocols can efficiently identify and close clinical gaps in care.
- Closing gaps in care improves patient outcomes and reduces costs.
- A wired advanced pharmacy environment enables measurement; makes prescribers, patients, and pharmacies accountable; and delivers transparency to payers.

Medco is committed to sharing what it has learned. The company will publish its research findings in peer-reviewed journals and share the results at professional conferences. Medco has already begun evaluating ways in which we can work with community pharmacies to bring the benefits and solutions we have created in the therapeutic centers to the patients they serve. And Medco is also working with policymakers in Washington in the hope that Medco Therapeutic Resource Centers can serve as a model contributing to the healthcare reform efforts under consideration today.

PRESCRIPTIONS FOR REFORM

Here are three action steps we can all take to foster meaningful healthcare reform:
- **Promote a common health information technology (HIT) platform.** Support the development of a common platform to share essential data with all who are involved in healthcare delivery. Robust wiring will promote transparency and improve communication. Key to the success of the wiring effort will be government involvement to set rules to promote open software platforms that can easily accommodate new and improved applications so that competition and flexibility will encourage innovation and ultimately lower costs. E-prescribing is a key component of a wired system that has proven benefits for pharmacy and healthcare.
- **Encourage widespread adoption of protocol-driven care.** In a wired system, protocols can be seamlessly incorporated to improve the effectiveness, efficiency, and safety of care delivery. Results can be monitored to assess clinical outcomes, and protocols can be modified based on new data or study results.
- **Incent providers to adopt HIT systems and protocol-driven care.** Support reforms that target physician and facility reimbursement. This will facilitate e-prescribing and systematic use of evidence-based protocols. Improved outcomes and reduced costs will then follow in time.

Working together, stakeholders are:
- Harnessing the power of technology.
- Connecting communities of practice.
- Driving the use of evidence-based protocols.
- Leveraging measurement to foster accountability.
- Rapidly integrating new science into current practice.
- Empowering patients to become value-conscious healthcare consumers.

These are the building blocks advancing the practice of pharmacy. They are also the tools that can be used in a broader context to drive meaningful reform across all of healthcare.
REFERENCES

EXECUTIVE SUMMARY


SPOTLIGHT ON TREND FOR 2008 | UNIT COST VS. UTILIZATION

THE DYNAMICS OF FUTURE TREND | GENERICS VS. SPECIALTY DRUGS


Among the insights revealed in this year’s report:

- average drug trend of 3.3%—a small increase from our all-time low in 2007.
- Pharmacogenomics collaborations with the Mayo Clinic and other leading institutions, we are forming a foundation for greater mail penetration had an average trend of -0.7%, while clients with less than 40% mail penetration had an average trend of 5.8%.
- Branded drug price inflation and unit-cost growth will be moderated by the wave of first-time generics in high-cost categories, which is expected to peak after 2011.

We would like to underscore a finding that reinforces mail as a successful quality and cost strategy: Clients with 40% or greater mail penetration had an average trend of -0.7%, while clients with less than 40% mail penetration had an average trend of 5.8%.

During the past year, Medco has proven that evidence-based, protocol-driven pharmacy practice can help lead a clinical transformation. Our specialist pharmacists across 14 Medco Therapeutic Resource Centers® provide condition-specific patient care that is proven to close gaps in adherence and omission, and lower total healthcare costs. Linked to our evidence-driven solutions for the historic challenges ahead.

This year’s Drug Trend Report explores the many forces both driving and moderating trend—including the economic crisis, emerging technologies, and the continued growth of specialty, biologic, and first-time generic drugs. It also provides a timely update on issues related to the urgent need for enlightened national healthcare reform—one of the most pressing public policy debates of our generation.

In this environment, we encourage you to collaborate with your account manager to closely monitor your plan performance and prepare for the changes and opportunities that lie ahead.

Sincerely,

David B. Snow, Jr.  Chairman and CEO
Robert S. Epstein, M.D., M.S.  Senior Vice President, Chief Medical Officer

PS For additional copies of this report, please contact your Medco account representative. A searchable PDF is available at www.drugtrend.com.

To our clients and friends:

We are pleased to share the Medco 2009 Drug Trend Report, which chronicles an unprecedented year and identifies solutions for the historic challenges ahead.

As predicted, specialty drug trend accelerated dramatically, from 12.4% in 2007 to 15.8% in 2008. In addition, the price inflation of branded pharmaceuticals increased more than 8%. Despite these trends, Medco clients in 2008 realized an average drug trend of 3.5%—a small increase from our all-time low in 2007.

Among the insights revealed in this year’s report:

- The weak economy drove renewed interest in generics, as the generic dispensing rate increased 4.4% to 64.1%.
- About 30% to 40% of the medicines currently in the pipeline are specialty drugs, with nearly 25% of those targeting very rare conditions.
- Biologic or protein-based drug therapies account for about 16% of prescription drug spending and are growing at a much faster rate than other drug categories.
- Branded drug price inflation and unit-cost growth will be moderated by the wave of first-time generics in high-cost categories, which is expected to peak after 2011.

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