WE WOULD LIKE TO ACKNOWLEDGE THE FOLLOWING PEOPLE FOR THEIR OUTSTANDING CONTRIBUTIONS TO
THE 2008 DRUG TREND REPORT:

Robert S. Epstein, M.D., M.S.
Jack A. Smith, M.A.
Linn Cattle, M.D.
Robert B. Verhugge, Ph.D.
Brad Epieisen
Gleni Hendling, M.S.
Bob Anthony
Libby McIl
Keith Bradbury, R.Ph., M.S.
Peter van Dijk
Kevin Cinary Pharm.D., M.B.A.
Bill Drellien, Pharm.D.
Mark Boyer
Valarie Trumor
Michael Elefonte

Publisher, Chief Medical Officer
Publisher, Chief Marketing Officer
Editor in Chief
Managing Editor; Senior Writer
Executive Creative Director
Creative Director
Brand Steward
Project Manager
Senior Writer
Senior Writer
Contributing Writer
Contributing Writer
Senior Editor
Contributing Editor
Senior Production Manager

Analytic support
Kai-C. Sham
Al DeCarlo
Susan Gassia, Ph.D., M.B.A.
Rose Healey
Tony Joseph
Thomas Kellerhouse, M.S., M.B.A.
Mona Kahlid, M.B.A.
Karmal Patel
Miriam Ryskin, M.S.
Jodi Schreiber
Hannah Solt, R.Ph., M.B.A.
Richard Thornton

Additional contributors
Peter Begens
Indrupal Bhandari, Ph.D.
Carolee Castieden, M.A.
Andrew Davis
Pattie Dodds
Woody Eisenberg, M.D.
Darnelle Fatigati
Susan Faust
David Rider
Tracy Grunfeld
Bill Head, J.D.
Scott Helmus
Jennifer Luddy
Ken Maloney, M.B.A.
Colleen Manley
Joe Marabito
Barbara S. Mero, M.P.H.
Michael Pollard, J.D., M.P.H.
Steve Russell, R.Ph.
Alexander Shielczyk, J.D., M.H.S.
Ann M. Smith, M.S.
Scott Straffon, M.P.H.
Anna Wong, M.P.H.

Account team contributors
Jody N. Allen, Pharm.D.
Francine Bellifonte, R.Ph., M.B.A.
Kim Brown
Jennifer Connery
Karen DeZeeuw, Pharm.D.
Patricia Felicai, M.B.A.
Candice Guglielmie
Matthew Pellela, M.B.A.
Alison Robertson
Maxine Sargent, R.Ph.
Jeff Scott

All rights in the product names, trade names, or logos of all third-party products appearing in this report, whether or not appearing with a trademark symbol, belong exclusively to their respective owners.

Medco, medco.com, Preferred Prescriptions, Rationaliq, and Medco Therapeutic Research Center are registered trademarks of Medco Health Solutions, Inc. All the Heart of Health and Rationaliq are trademarks of Medco Health Solutions, Inc.

© 2008 Medco Health Solutions, Inc. All rights reserved.

Designed and produced by regards.com.
To our clients and friends:

We are pleased to share the Medco 2008 Drug Trend Report, which documents an historic year and forecasts the challenges that we will be managing together in the years ahead.

By capitalizing on savings opportunities offered by generics and mail service, Medco clients in 2007 achieved an average drug trend of only 2%—our lowest rate ever. We believe this reflects the effectiveness of our collaborative efforts using the tools and techniques that are proven to significantly “beat the market.”

Among the insights revealed in this year’s report:
- The reversal in spending for lipid-lowering drugs, made possible by leveraging a record generic opportunity, was the largest factor in moderating trend.
- Specialty drugs now account for more than 11% of pharmacy plan spending, led by drugs that treat autoimmune conditions, cancer, and multiple sclerosis.
- More than 25 first-time generics are scheduled for market introduction over the next 3 years—allowing clients and members to continue harvesting the value of lower-cost medications.

Over the past year, Medco has continued to invest in its portfolio of services to improve your clinical and financial outcomes. This included the acquisition of Liberty Medical to deliver advanced care to the more than 4 million Medco patients with diabetes, which is now the largest single driver of drug trend. We have also launched innovative genetic-testing collaborations with the Mayo Clinic and LabCorp—making real the promise of personalized medicine. Our new genomic testing service builds on the Medco Therapeutic Resource Center® platform, which provides advanced, condition-specific care to patients.

Our Drug Trend Report examines the leading market forces that are transforming the healthcare landscape: information technology, consumerism, federal policy, and the expected explosion in new specialty medicines coming to market. Each has a pervasive influence on our industry, and we offer guidance on how to anticipate future changes and appropriately align your plan.

With the information in this report, we encourage you to meet with your account manager, who heads a team that has the skills and experience to help you model, manage, and monitor your prescription drug benefit—helping to ensure your continued success.

Sincerely,

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

P.S. If you would like additional copies of this report, please contact your Medco account representative. Electronic copies are available at www.drugtrend.com.
FOCUSBING ON TREND | A LOOK BACK AT 2007

The increased availability and use of generic medications had a dramatic effect on the rate of spending growth for prescription drugs in 2007. For Medco clients, drug trend averaged only 2.0%—the lowest rate ever.

Diabetes therapies have emerged as the leading driver of spending growth, followed closely by treatments for respiratory conditions and cancer. Spending declined sharply in therapeutic areas where blockbuster brands have come off patent during the past few years. Costs in the lipid-lowering class showed a remarkable decline in 2007, responding to the introduction of new generic statins in 2006.

Drug utilization grew at a moderate pace overall, but treatment rates increased rapidly for many neurological, urological, and autoimmune disorders. New safety concerns led to declining use of certain treatments for diabetes and anemia.

Unit costs grew slowly overall, as the increased use of low-cost generics helped offset rapid pricing growth for many brand-name drugs. Lower unit costs for Medicare-eligible plan members also helped moderate spending growth.

Spending for specialty drugs increased 12.3% in 2007, driven primarily by the increased cost of treatments for autoimmune disorders, cancer, and multiple sclerosis. Specialty trend is dominated by the expanding use of high-cost biologics in therapeutic areas where few treatment alternatives are available.
Our extended forecast calls for continued moderate growth in prescription drug spending over the next 3 years. Plans will continue to be buffeted by updrafts from new, high-cost biologics, but these forces will be moderated by strong downward pressure from an expanding array of low-cost generics.

Treatments for cancer, infectious diseases, and central nervous system disorders are the leading areas of new drug development. Exciting new therapies are also being developed for cardiovascular conditions, diabetes, osteoporosis, and autoimmune disorders. Some of these drugs will be targeted toward smaller populations and will be accompanied by diagnostic tests to help identify patients most likely to benefit.

A new wave of first-time generics will moderate the growth in unit costs. Drugs with total U.S. sales of nearly $24 billion could lose patent protection over the next 3 years, expanding the market for lower-cost generics. New generics are expected to reduce trend in several therapeutic areas, including epilepsy, osteoporosis, and gastrointestinal disorders.

Specialty drugs will continue to be leading drivers of trend. In the near term, generic alternatives will not be available for most of these drugs. Over time, biosimilar versions may become available, offering opportunities to reduce the impact of brand inflation on spending growth.

Over the next 10 years, the American healthcare system will be transformed by revolutionary changes in information technology, consumer involvement, benefit management, federal policy, and the biologic sciences. These changes will offer new opportunities to improve the safety and quality of care, but the net effects on cost will vary widely. Anticipating these changes will help plan sponsors prepare for the future before it happens.

Advances in information technology will be a major accelerator of change. New technologies for social networking and personal health records are already beginning to reshape how patients access healthcare information. New federal mandates and incentives will increase the adoption of electronic prescribing systems, improving medication safety and reducing costs.

Benefit management will be transformed by the availability of new tools for integrating medical and pharmacy data, increasing generic drug utilization, and managing the rising costs of specialty drugs. New federal programs will have a major impact on the availability of healthcare coverage for all Americans and the adoption of value-based purchasing.

The practice of medicine will be transformed by pharmacogenomic testing, follow-on biologics, new cancer vaccines, and new drugs based on RNA interference. Personalized medicine will be adopted widely to help optimize the selection of drugs and dosages for individual patients.
FOCUSING ON TREND

A LOOK BACK AT 2007
Looking back at 2007, you will gain insight into:

- **The key forces that shaped prescription drug trend in 2007.**
  A large wave of first-time generics helped offset the impact of specialty drugs, yielding a remarkably low rate of spending growth for prescription benefit plans.

- **Treatment areas that are emerging as the leading drivers of trend.**
  Unit costs grew rapidly for brand-dominated drug classes—such as diabetes, asthma, and cancer drugs. Increased use of generic drugs, including the new statins, kept price inflation low. Utilization grew rapidly in many therapeutic areas, but declined in others due to emerging safety concerns.

**FOCUSBING ON TREND | A LOOK BACK AT 2007**

**A lens on trend**

In 2007, the era of generic medications reached full stride. Over the past 2 years, generics have become available for many blockbuster brand-name drugs, providing unprecedented opportunities for benefit plans and their members to lower the cost of pharmaceutical care. Generics are now the predominant form of therapy for patients with prescription drug benefits; in the fourth quarter of 2007, generics accounted for more than 61% of the prescriptions dispensed for plan members.

As older brand-name medications become available in generic form, the market for newer, high-cost specialty medications continues to expand. Several new biotechnology drugs were approved in 2007, and the use of specialty drugs continued to grow at a rapid pace. In some therapeutic areas, high-cost biologics have emerged as the therapies of choice, and biogeneric versions of these drugs are not yet available.

2007 was also a year for managing the fundamentals—capitalizing on the value offered by generic drugs, preferred brands, mail service, and specialty pharmacy services. Working with Medco, plan sponsors have expanded their use of these opportunities to manage costs while maintaining or improving the quality of care, both in traditional benefit plans and in the newer plans defined under Medicare Part D.

The net result of these forces—new generics, specialty drugs, and careful plan management—was a remarkably slow rate of spending growth in 2007. For Medco clients, the average cost of prescription drug benefits increased only 2.0% in 2007, continuing the pattern of moderate growth that has characterized the past few years. Drug trend has declined sharply from the double-digit rates that were typical in the years prior to 2004.
KEY DRIVERS

The primary contributors to drug trend are utilization and unit cost. In 2007, unit costs grew slowly (0.4%) and trend was dominated by an overall increase in utilization (1.6%).

- **Utilization** is the amount of medication obtained by members of a plan. Utilization can increase if more plan members begin taking medication (an increase in users) or if current users take more medication (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).

The utilization growth in 2007 was largely due to an increase in the number of members receiving medication treatment for long-term conditions. Growth was especially rapid for drugs used to treat neurological, urological, and autoimmune disorders. Utilization declines in a few therapeutic categories helped offset this growth.

- **Unit cost** is the plan’s cost per unit of therapy. Unit costs will grow if drug prices increase (price inflation), and unit costs will 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 2007, unit-cost growth was driven by price increases for single-source brand-name drugs and shifts toward higher-cost therapies in some categories. These strong inflationary pressures were offset by a significant increase in the use of lower-cost generic drugs and plan-preferred brands. The net result was a very low rate of unit-cost growth overall.

---

Figure 1. National healthcare costs in 2007
Source: Centers for Medicare & Medicaid Services

Figure 2. Top contributors to growth of national healthcare spending
Source: Centers for Medicare & Medicaid Services

---

*Reported trends are based on 2 years’ data on pharmaceutical spending, representing 82% of the $43.9 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” (PEPM) basis, unless otherwise specified. An “eligible” is a household, which may include multiple members who are covered under the plan. 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.*
**NATIONAL TREND**

Prescription drug purchases account for about 10% of national healthcare spending (Figure 1), and they represent more than 10% of the projected growth in national healthcare costs in 2007 (Figure 2). Healthcare spending growth is dominated by the rising costs of hospital care and physician services, which together account for more than 50% of national healthcare trend (Figure 2).

For many years, prescription drug spending was the fastest-growing component of national healthcare costs, but during the past few years the pace of growth has slowed considerably (Figure 3). National growth rates for prescription drug spending showed a one-time spike in 2006 with the introduction of Medicare Part D, which extended prescription drug coverage to millions of previously uninsured Americans.

According to projections by the Centers for Medicare & Medicaid Services (CMS), national drug trend for 2007 is estimated at 6.7%—slower than the growth rates for hospital care and home healthcare services. However, spending on prescription drugs is likely to accelerate over the next several years, as rapid utilization growth more than offsets the expanding availability of generic drugs. As a result, national drug trend is expected to outpace the trend for other major contributors to national healthcare costs, beginning in 2010 (Figure 3).

Figure 3. National healthcare cost trends from 2003 to 2015
Source: Centers for Medicare & Medicaid Services

---

**FOCUSING ON TREND | A LOOK BACK AT 2007**

**Unit costs: The power of generics**

The expanding availability and acceptance of generic medications is transforming pharmaceutical care. For plan sponsors, generic drugs offer a welcome opportunity to reduce plan costs while continuing to provide effective care. Generics offer the safety and efficacy of their brand-name counterparts at a fraction of the cost.

**CATCHING THE WAVE**

Over the past few years, dozens of new generic drugs have become available as a result of patent expirations, “at-risk” launches, and successful patent challenges. The pace of generic drug introductions quickened during 2006 and 2007, as several blockbuster brands became available in generic form for the first time.
During 2006, the generic conversions of four blockbuster medications—Flonase® (fluticasone), Pravachol® (pravastatin), Zocor® (simvastatin), and Zoloft® (sertraline)—offered major new opportunities for cost savings through generic substitution. These generics had an initial impact on trend in 2006 and a dramatic impact on trend in 2007, their first full year of availability. The combined U.S. market opportunity for all of the new generics approved in 2006 exceeded $16 billion (based on prior-year sales for the corresponding brands).

An additional wave of blockbuster drugs became available in generic form during 2007—including Norvasc® (amlodipine besylate), Lotrel® (amlodipine besylate/benazepril), Ambien® (zolpidem), Coreg® (carvedilol), and Toprol-XL® (metoprolol succinate extended-release; 50 mg, 100 mg, 200 mg). The primary generic drug introductions during 2007 are shown in Table 1. These first-time generics all reduced unit costs in their therapeutic classes, especially the generics that were introduced before the last few months of the year. The combined U.S. market opportunity for all of the new generics approved in 2007 exceeded $13.8 billion.

Table 1. First-time generic drugs introduced during 2007
Source: U.S. Food and Drug Administration4; IMS (retail sales)5

<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 2006 ($M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1Q 2007</td>
<td>Duragesic® 12</td>
<td>fentanyl transdermal system 12.5 mcg/hr propranolol extended-release capsules</td>
<td>Pain (all branded strengths)</td>
<td>$427</td>
</tr>
<tr>
<td></td>
<td>Inderal® LA</td>
<td>amlodipine besylatea</td>
<td>High blood pressure</td>
<td>$182</td>
</tr>
<tr>
<td></td>
<td>Norvasc®</td>
<td>High blood pressure</td>
<td>$2.331</td>
<td></td>
</tr>
<tr>
<td>2Q 2007</td>
<td>Ambien® Omnicefb</td>
<td>zolpidem tablets cefdinir capsules and oral suspensionb</td>
<td>Insomnia</td>
<td>$2,180</td>
</tr>
<tr>
<td></td>
<td>Toprol-XL®</td>
<td>metoprolol succinate extended-release 50-mg, 100-mg, and 200-mg tabletsd</td>
<td>Bacterial infection</td>
<td>$900</td>
</tr>
<tr>
<td></td>
<td>Lotrel®</td>
<td>amlodipine besylate/benazepril tabletsd</td>
<td>High blood pressure, angina, congestive heart failure (CHF)</td>
<td>$1,200</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3Q 2007</td>
<td>Lamisil® Protonix®</td>
<td>terbinafine tablets pantoprazolec</td>
<td>Nail fungal infections</td>
<td>$802</td>
</tr>
<tr>
<td></td>
<td>Famvir® Coreg®</td>
<td>famciclovir tabletsf</td>
<td>Gastroesophageal reflux disease, ulcers</td>
<td>$2,262</td>
</tr>
<tr>
<td></td>
<td></td>
<td>carvedilol tablets</td>
<td>Herpes virus infections</td>
<td>$186</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High blood pressure, CHF</td>
<td>$1,283</td>
</tr>
<tr>
<td>4Q 2007</td>
<td>Trileptal® Estrostepe® Fe</td>
<td>oxcarbazepine tablets norethindrone/ethinyl estradiol/ferrous fumarate tablets</td>
<td>Seizures</td>
<td>$601</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Birth control</td>
<td>$130</td>
</tr>
</tbody>
</table>

Note: The table shows first-time generics launched in 2007 for brands with prior-year market sales greater than $125 million. FDA approval may not imply generic availability.

* Mylan Laboratories introduced amlodipine besylate tablets in 2.5-mg, 5-mg, and 10-mg formulations. Mylan received final FDA approval for its generics on October 2, 2005, but did not launch them until March 23, 2007.

* Teva received FDA approval for the generic products and launched them at risk, due to ongoing patent litigation. Abbott authorized DAVA Pharmaceuticals to distribute generic cefdinir capsules and suspension. This is not a patent expiration.

* KV and Par launched generic metoprolol succinate extended-release in the 100-mg and 200-mg strengths on July 26, 2007, and Sandoz and Par launched generics in the 50-mg strength on August 3. Par’s generics are authorized generics from AstraZeneca. Generic metoprolol succinate extended-release 25-mg tablets received approval and were launched in November 2006.

* Teva began shipping their generic amlodipine besylate/benazepril tablets after receiving final FDA approval on May 18, 2007. The following day, the U.S. District Court for the District of New Jersey granted a temporary order restraining Teva’s launch. The temporary restraining order was lifted on June 11, and Teva immediately resumed distribution of the generic. This is an at-risk launch due to ongoing patent litigation and is not a patent expiration.

* FDA approved Teva’s generic pantoprazole on August 3, 2007. Teva launched its generic at risk on December 23. Three days later, Teva agreed to cease sales of the generic while it negotiates a settlement with Wyeth. This is not a patent expiration.

* After a brief at-risk launch, Teva was temporarily prohibited from selling its generic famciclovir. The U.S. Court of Appeals for the Federal Circuit later denied Novartis’s emergency motion for an injunction, allowing Teva to resume at-risk sales of its generic famciclovir tablets. Teva has been awarded a 180-day period of marketing exclusivity for generic famciclovir. Novartis maintains that various U.S. patents related to Famvir are valid until 2015.
The adoption of generic medications in clinical practice has increased rapidly. Generic drugs now account for the majority of prescriptions filled for plan members. In 2007, the average generic dispensing rate for Medco clients was 59.7%—a significant increase over the 55.2% rate in 2006.

Benefit plans vary widely in the average level of generic drug utilization by their members (Figure 4). The wide variations in generic dispensing rates are due to differences in formulary design, plan demographics, and the use of plan management tools to encourage members and physicians to select generic drugs. The majority of plans achieved generic dispensing rates between 59% and 64% in the fourth quarter of 2007, but plans with stronger generic incentive programs achieved generic dispensing rates as high as 67% to 72%. The average generic dispensing rate for Medco clients in the fourth quarter of 2007 was 61.4%.

Many plans encourage the use of generic drugs by setting lower co-payment or coinsurance levels for generics than for brands. Some plans have also introduced programs that offer temporary waivers of the co-payments that usually apply to generic drugs. Although these waiver programs may increase the plan’s share of costs (on a percentage basis), the goal for many plans is to reduce overall expenditures by shifting utilization toward drugs that have a lower net cost.

**CAPITALIZING ON FIRST-TIME GENERICS**

By promoting the use of newly introduced generics, benefit plans can achieve a one-time savings in the first year and sustained savings in the years that follow. Capitalizing on this opportunity requires an efficient process for generic substitution. Medco and its clients have used a variety of strategies to expedite these market transitions, including alerts to physicians, messages to members, and adjustments to formularies, plan designs, and coverage rules.

Because of these efforts, changes in drug selection tend to occur very rapidly after the introduction of a first-time generic. For example, when generic versions of Ambien® (zolpidem) became available in April 2007, prescription volumes for the brand-name drug declined rapidly as the new generics became the dominant choice (Figure 5). During the first 30 days after the launch of the generic products, the brand-name product lost 87.0% of its overall market share to the new generics—85.6% at retail and 97.2% at mail.
The changeover to a new generic may have a limited impact during the year of the transition, especially if it occurs late in the year, but it can have a large impact on unit costs during the following year. For example, the combined unit costs for Zoloft and generic sertraline (introduced in August 2006) were only 7% lower in 2006 than in 2005. However, unit costs dropped sharply in 2007, the first full year of generic availability. The combined unit costs for Zoloft and generic sertraline were 53% lower in 2007 than in 2006.

The transition to a new generic generally occurs more quickly at mail (compared with retail), because generic interchange programs are an integral part of prescription processing by Medco’s mail-order pharmacy. For example, within the first week of the introduction of generic zolpidem, Medco’s mail-order pharmacy achieved a generic substitution rate of 96.9%, compared with a 76.6% substitution rate for the same period at retail.

**IMPACT OF SHARE EROSION**

In advance of a scheduled patent expiration, brand manufacturers often launch new patent-protected products in an effort to retain or grow their market share in the class. Strong brand marketing, including direct-to-consumer advertising, can drive market share toward new brand-name drugs, reducing the share of older brand-name drugs before they go off patent.

Market share erosion can make it difficult for plan sponsors to capitalize on the introduction of generic versions of a brand-name drug. Share erosion reduces the base of brand users, limiting the opportunities for generic substitution when the generics become available.

The generic conversion of Ambien provides an excellent example of the challenges posed by share erosion. Ambien lost significant market share before generic versions were introduced, while market share grew for new brand-name products, such as Lunesta®, which were heavily advertised to American consumers. Ambien accounted for almost 70% of sedative-hypnotic prescriptions in the United States in early 2005, but its market share had declined to only 43% by the end of 2006. This decline sharply reduced the potential savings when generic versions for Ambien were introduced in 2007, since the base for generic substitution was significantly lower than it otherwise would have been.
Many of the new brands that compete with generics are follow-on versions of the original brands. Some follow-on products, like Ambien CR®, are new formulations of the original brand, and some are chemical modifications of the original compound. Follow-on products are one of the strategies used by brand manufacturers to protect their patent franchise and resist the market movement toward generics.

THE EVERGREEN CHALLENGE

Pharmaceutical manufacturers use multiple strategies to prolong their franchise on a drug product. These strategies are often referred to as evergreening. Typically, a manufacturer will introduce a new version of a product as it approaches patent expiration, but before the patent actually expires. This strategy allows the manufacturer to move patients to the newer version before the older version goes generic. The transition may be achieved by marketing the new product intensively, raising the price of the older product, or removing the older product from the market.

To extend the patent life of an existing compound, manufacturers may take one or more of the following approaches:

- Develop a single-isomer version of a racemic compound. For example, Xyzal® (levocetirizine, introduced in May 2007) is a single-isomer version of Zyrtec® (cetirizine).
- Introduce an active metabolite of an existing product. For example, Pristiq™ (desvenlafaxine, approved in February 2008) contains an active metabolite of Effexor XR® (venlafaxine).
- Develop a once-daily, extended-release version of a product. For example, Seroquel XR™ (introduced in May 2007) is an extended-release version of Seroquel® (quetiapine).
- Obtain a new indication for a product and market it under a different brand name. For example, Revatio® includes the same active ingredient as Viagra® (sildenafil), but was approved for a different indication in a different dosage strength.
- Introduce a new combination product. For example, Caduet® combines the active ingredients in Lipitor® (atorvastatin) and Norvasc (amlodipine besylate).
- Add another molecule to the basic drug to extend its half-life. For example, Neulasta® (pegfilgrastim) is a pegylated version of Neupogen® (filgrastim).

In many cases, follow-on products do not have distinct therapeutic advantages over the older compounds, although they may offer greater convenience or improved compliance through less frequent dosing. However, in a few cases, follow-on products provide a clear therapeutic advantage over the older versions; for example, pegylated alfa interferons are generally more effective than standard alfa interferons.

Drug product evergreening is a routine part of drug life-cycle management. As new follow-on products enter the market, they complicate the efforts of plan sponsors to capitalize on the introduction of lower-cost generics.

ECONOMIC POWER

The financial impact of a generic conversion is based on three market realities:

1. **Low 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 close 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 to 80% or more below the price of the brand.

2. **Low price inflation.** Prices for generic drugs increase more slowly than prices for brand-name drugs. In 2007, 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 7.4%.
3. **Deeper discounts.** Generic drugs can generally be purchased at deeper discounts off wholesale prices than brand-name drugs. Improving generic drug discounts through volume purchasing and increased utilization is a key factor in controlling price inflation.

As generic dispensing increases, average unit costs grow more slowly because of the lower inflation rate for these products. In therapeutic classes with few or no generic drug options, unit costs are primarily affected by price increases for brand-name drugs or shifts in product mix toward higher-cost brands. In therapeutic classes with a broad selection of generics, unit costs grow more slowly as market competition stabilizes or reduces the prices for generic drugs.

**FOCUSING ON TREND | A LOOK BACK AT 2007**

**Utilization: Trends in treatment**

Utilization growth averaged only 1.6% in 2007. Treatment rates increased rapidly for many long-term conditions, including autoimmune disorders and Alzheimer’s disease, but utilization grew slowly or declined for many other commonly treated conditions.

**DAYS AND USERS**

For each therapeutic class, utilization growth is a combination of two types of changes—changes in treatment rate (users) and changes in treatment intensity (days). Treatment rate measures the number of people who use medications to treat a given condition. Treatment intensity measures the average number of treatment days per year.

Treatment rates increased most dramatically for rheumatological drugs and many classes of neurological drugs, especially those used to treat Alzheimer’s disease, Parkinson’s disease, attention deficit hyperactivity disorder (ADHD), and seizure disorders (Figure 6). Several classes of neurological drugs showed a strong increase in treatment intensity, including sedative/hypnotics, antipsychotics, and treatments for Alzheimer’s and Parkinson’s diseases.

Lipid-lowering therapies also showed rapid growth in treatment rate (3.0%) and treatment intensity (3.3%), reflecting the trend toward more intensive treatment of elevated cholesterol and triglyceride levels.

For other widely used classes of drugs for long-term conditions, treatment rates grew slowly or showed moderate declines. Treatment rates grew slowly for diabetes medications (1.6%) and cancer and transplant medications (0.1%), and they declined slightly for antihypertensives (−0.7%) and gastrointestinal

**Figure 6. Changes in utilization for selected therapeutic classes in 2007**

Source: Medco data

Note: The figure shows the contribution of treatment rate (users) and treatment intensity (days) to utilization growth in 2007. Users are measured on a per-member basis, and therapy days are measured per user per year. Therapeutic classes are rank-ordered from the largest utilization growth (at the top) to the largest utilization decline (at the bottom). Select neurological includes treatments for Alzheimer’s and Parkinson’s diseases.
medications (–2.0%). However, in all of these cases, the average days of medication use increased. Treatment intensity increased for antihypertensives (1.8%) and diabetes medications (1.0%), reflecting clinical trends toward more intensive therapy and the use of multiple drugs to achieve clinical targets.

For therapies that are often used on a short-term or intermittent basis, overall utilization increased most strongly for sedative/hypnotics, narcotic pain relievers, and antiviral medications.

Given the wide variations across therapeutic classes, it is unlikely that any single factor accounted for the pattern of utilization growth in 2007. Each therapeutic area is affected by a unique mix of clinical, regulatory, and market forces—including drug safety issues, clinical practice changes, new drug introductions, and new indications.

### DRUG SAFETY

In several therapeutic areas, heightened awareness of safety risks has led clinicians to be more cautious in prescribing certain types of medications, resulting in an overall decline in use. Two of the most prominent therapeutic areas over the past few years have been the cyclo-oxygenase-2 (COX-2) inhibitors and hormone replacement therapies. During 2007, safety concerns emerged in several new therapeutic areas, including drug treatments for diabetes and anemia. In all of these therapeutic areas, clinical assessments of the balance between risk and benefit have changed over time.

- **Nonnarcotic pain relievers.** Concerns over the potential cardiovascular risks of COX-2 inhibitors led to a sharp reduction in the use of nonnarcotic pain relievers in 2005 and 2006, after the market withdrawals of Vioxx® (September 2004) and Bextra® (April 2005).10,11 Some users shifted to traditional nonsteroidal anti-inflammatory drugs (NSAIDs) or to Celebrex®, but many discontinued use of all products in this class or reduced their intensity of use. The decline in utilization continued during 2007, although at a much more moderate rate. Treatment rates for nonnarcotic pain relievers declined 0.3%, and the average days of use declined 2.0%.

- **Hormone replacement therapy.** Safety concerns raised by findings from the Women’s Health Initiative and other studies have led to a continuous decline in the use of hormone replacement therapies over the past 6 years.12-15 Although more recent data are beginning to shift the balance of safety considerations,16 treatment rates continued to decline in 2007.

- **Thiazolidinediones (TZDs).** A new safety concern emerged in 2007 after reports were issued about an increased risk of heart attacks in patients who use Avandia® (rosiglitazone), an oral medication for the treatment of type 2 diabetes.17 In May 2007, the Food and Drug Administration (FDA) issued an alert regarding a possible increased risk of heart attack and heart-related deaths among patients taking Avandia.18 After reviewing postmarketing adverse event reports, the FDA requested that a black box warning on the risk of heart failure be added to the labeling for all products containing TZDs—Avandia, Actos®, and related combination products.19 The safety alert in May 2007 triggered a rapid drop in Avandia prescription rates, as clinicians shifted to other treatment options for many patients with type 2 diabetes. By the end of 2007, prescription volumes for Avandia had dropped more than 60% from their levels earlier in the year.

- **Erythropoiesis-stimulating agents (ESAs).** In March 2007, the FDA issued a public health advisory about potential risks associated with ESAs (Aranesp®, Epogen®, and Procrit®).20 These drugs are widely used to treat anemia in patients who have renal failure or who are receiving chemotherapy. In May 2007, an FDA advisory committee recommended more restrictive guidelines in product labeling to reduce the risk of adverse events.21 In response to these recommendations, many plans have adjusted their coverage criteria for ESAs—for example, setting lower maximum hemoglobin targets or limiting coverage to 3 months after the end of chemotherapy. The net result of these heightened safety concerns was a 12% year-over-year decline in utilization of ESAs.
**DRUG INNOVATION**

**New drugs**

In 2007, the FDA approved 16 new molecular entities (NMEs) and 7 new biologics (Table 2). These include several new specialty drugs for the treatment of cancer, pulmonary arterial hypertension, and other conditions. In addition to these 23 new drugs and biologics, the FDA also approved many applications for new dosage forms, new combinations, and new salts of existing drugs.25

The first-year impact of these new drugs on utilization was relatively small, since some were introduced late in the year and many are indicated for low-prevalence conditions. However, several of the new drugs approved in 2005 and 2006 had a significant impact on utilization growth in 2007. Examples are Byetta® and Januvia® (for diabetes), Revlimid® (for myelodysplastic syndromes), and Sutent® (for cancer).

Table 2. New drug and biologic introductions in 2007

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Brand name</th>
<th>Generic name</th>
<th>Type</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1Q 2007</td>
<td>Vyvanse™</td>
<td>lisdexamfetamine</td>
<td>NME</td>
<td>Attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td></td>
<td>Tekturna®</td>
<td>aliskiren</td>
<td>NME</td>
<td>High blood pressure</td>
</tr>
<tr>
<td></td>
<td>Tykerb®</td>
<td>lapatinib</td>
<td>NME</td>
<td>HER2-positive breast cancer</td>
</tr>
<tr>
<td></td>
<td>Soliris®</td>
<td>eculizumab</td>
<td>TB</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td></td>
<td>Ceprotin™</td>
<td>protein C concentrate, human</td>
<td>B</td>
<td>Prevention and treatment of venous thrombosis in patients with severe congenital protein C deficiency</td>
</tr>
<tr>
<td>2Q 2007</td>
<td>Altabax®</td>
<td>retapamulin</td>
<td>NME</td>
<td>Impetigo</td>
</tr>
<tr>
<td></td>
<td>Influenza virus vaccine, H5N1</td>
<td>influenza virus vaccine, H5N1, inactivated</td>
<td>B</td>
<td>Immunization against avian influenza (“bird flu”)</td>
</tr>
<tr>
<td></td>
<td>Neupra®</td>
<td>rotigotine</td>
<td>NME</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td></td>
<td>Torisel™</td>
<td>temsirolimus</td>
<td>NME</td>
<td>Advanced renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Letairis™</td>
<td>ambrisentan</td>
<td>NME</td>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>3Q 2007</td>
<td>Selzentry™</td>
<td>maraviroc</td>
<td>NME</td>
<td>HIV-1 infection</td>
</tr>
<tr>
<td></td>
<td>Ammonia N-13</td>
<td>ammonia N-13</td>
<td>NME</td>
<td>Diagnostic agent for positron emission tomography</td>
</tr>
<tr>
<td></td>
<td>Evithrom™</td>
<td>topical thrombin, human</td>
<td>B</td>
<td>Control of bleeding when standard surgical techniques are ineffective or impractical</td>
</tr>
<tr>
<td></td>
<td>Somatuline® Depot</td>
<td>lanreotide</td>
<td>NME</td>
<td>Acromegaly</td>
</tr>
<tr>
<td></td>
<td>ACAM2000™</td>
<td>smallpox vaccine, live</td>
<td>NME</td>
<td>Immunization against smallpox</td>
</tr>
<tr>
<td></td>
<td>Afluria®</td>
<td>influenza virus vaccine</td>
<td>B</td>
<td>Seasonal influenza vaccine</td>
</tr>
<tr>
<td>4Q 2007</td>
<td>Doribax™</td>
<td>doripenem</td>
<td>NME</td>
<td>Bacterial infections</td>
</tr>
<tr>
<td></td>
<td>Ixempra™</td>
<td>ixabepilone</td>
<td>NME</td>
<td>Breast cancer</td>
</tr>
<tr>
<td></td>
<td>Tasigna®</td>
<td>nilotinib</td>
<td>NME</td>
<td>Philadelphia chromosome–positive chronic myelogenous leukemia</td>
</tr>
<tr>
<td></td>
<td>Isentress®</td>
<td>raltegravir</td>
<td>NME</td>
<td>HIV-1 infection</td>
</tr>
<tr>
<td></td>
<td>Mircea®</td>
<td>methoxy polyethylene glycol-epoetin beta</td>
<td>TB</td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Bystolic™</td>
<td>nebivolol</td>
<td>NME</td>
<td>High blood pressure</td>
</tr>
<tr>
<td></td>
<td>Kuvan™</td>
<td>sapropterin</td>
<td>NME</td>
<td>Phenylketonuria</td>
</tr>
</tbody>
</table>

Note: The table shows new prescription drugs approved by the FDA during 2007. Three types of new drugs are shown:

- NME: New molecular entity
- TB: Therapeutic biologic (approved by the Center for Drug Evaluation and Research)
- B: Biologic (approved by the Center for Biologics Evaluation and Research)

Bold text indicates specialty drugs.

*Priority review

¹Launch of Mircea may be significantly delayed due to a court ruling that it infringes Amgen's patents for Epogen® and Aranesp®.
New indications

As the rate of new drug approvals has slowed, manufacturers have focused increasingly on new indications for current products as a means of expanding their markets. Although off-label use of a drug for a new indication may occur before the indication is approved, FDA approval permits a manufacturer to advertise the new indication to physicians and consumers. Some of the principal new indications approved during 2007 are shown in Table 3. Many of these drugs were significant drivers of utilization growth in 2007.

Table 3. New indications approved in 2007
Source: U.S. Food and Drug Administration

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Brand name</th>
<th>Generic name</th>
<th>Uses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1Q 2007</td>
<td>Yaz®</td>
<td>drospirenone/ethinyl estradiol</td>
<td>Treatment of moderate acne in women</td>
</tr>
<tr>
<td></td>
<td>Alphanate®</td>
<td>antihemophilic factor/ von Willebrand factor complex, human</td>
<td>Prevention of excessive bleeding in surgical and/or invasive procedures in patients with von Willebrand’s disease</td>
</tr>
<tr>
<td></td>
<td>Cymbalta®</td>
<td>duloxetine</td>
<td>Treatment of generalized anxiety disorder</td>
</tr>
<tr>
<td></td>
<td>Humira®</td>
<td>adalimumab</td>
<td>Treatment of moderate to severe Crohn’s disease</td>
</tr>
<tr>
<td></td>
<td>Lipitor®</td>
<td>atorvastatin</td>
<td>Reduction in risk of heart attack, stroke, angina, revascularization procedures, and hospitalization for CHF</td>
</tr>
<tr>
<td></td>
<td>Keppra®</td>
<td>levetiracetam</td>
<td>Treatment of generalized tonicoclonic seizures in adults and children</td>
</tr>
<tr>
<td></td>
<td>Rhophylac®</td>
<td>Rh$_{(D)}$ immune globulin intravenous, human</td>
<td>Treatment of Rh$_{(D)}$ positive, nonsplenectomized patients with chronic immune thrombocytopenia purpura</td>
</tr>
<tr>
<td>2Q 2007</td>
<td>Singularair®</td>
<td>montelukast</td>
<td>Prevention of exercise-induced bronchoconstriction</td>
</tr>
<tr>
<td></td>
<td>Reclast®</td>
<td>zoledronic acid</td>
<td>Treatment of Paget’s disease</td>
</tr>
<tr>
<td></td>
<td>Humate-P®</td>
<td>antihemophilic factor/ von Willebrand factor complex, human</td>
<td>Prevention of excessive bleeding pre- and post-surgery in patients with von Willebrand’s disease</td>
</tr>
<tr>
<td></td>
<td>Fragmin®</td>
<td>dalteparin</td>
<td>Extended treatment (up to 6 months) of symptomatic venous thromboembolism</td>
</tr>
<tr>
<td></td>
<td>Lovenox®</td>
<td>enoxaparin</td>
<td>Treatment of acute ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Norditropin®</td>
<td>somatropin (rDNA origin)</td>
<td>Treatment of short stature in children with Noonan’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Lyrica®</td>
<td>pregabalin</td>
<td>Management of fibromyalgia</td>
</tr>
<tr>
<td>3Q 2007</td>
<td>Reclast®</td>
<td>zoledronic acid</td>
<td>Treatment of osteoporosis in postmenopausal women</td>
</tr>
<tr>
<td></td>
<td>Risperdal®</td>
<td>risperidone</td>
<td>Treatment of pediatric schizophrenia and bipolar I disorder</td>
</tr>
<tr>
<td></td>
<td>Keppra®</td>
<td>levetiracetam</td>
<td>Treatment of myoclonic seizures in adults with juvenile myoclonic epilepsy</td>
</tr>
<tr>
<td></td>
<td>Evista®</td>
<td>raloxifene</td>
<td>Reduction in risk of invasive breast cancer in postmenopausal women</td>
</tr>
<tr>
<td></td>
<td>Norditropin®</td>
<td>somatropin (rDNA origin)</td>
<td>Treatment of short stature in children with Turner’s syndrome</td>
</tr>
<tr>
<td>4Q 2007</td>
<td>Abilify®</td>
<td>aripiprazole</td>
<td>Treatment of pediatric schizophrenia</td>
</tr>
<tr>
<td></td>
<td>Crestor®</td>
<td>rosvastatin</td>
<td>Slowing of the progression of atherosclerosis in adults</td>
</tr>
<tr>
<td></td>
<td>Zyrtec® and Zyrtec-D®</td>
<td>cetirizine and cetirizine/ pseudoephedrine</td>
<td>Switch to over-the-counter status</td>
</tr>
<tr>
<td></td>
<td>Abilify®</td>
<td>aripiprazole</td>
<td>Adjunctive treatment for major depressive disorder</td>
</tr>
<tr>
<td></td>
<td>Effexor® XR</td>
<td>venlafaxine extended-release</td>
<td>Long-term treatment of social anxiety disorder</td>
</tr>
</tbody>
</table>

Note: The table shows some of the efficacy supplements approved by the FDA during 2007.
*Consult product label for the exact wording of the indications for these products.
Bold text indicates specialty drugs.
Prism on trend: The drivers of cost

Drug spending in 2007 was dominated by a few broad therapeutic categories: central nervous system (CNS), cardiovascular, gastroenterology, respiratory/allergy, endocrine/diabetes, anti-infectives, and musculoskeletal/rheumatology. These seven therapeutic categories were responsible for 84% of total drug spending during 2007 (Figure 7).

The therapeutic classes that had the largest impact on trend are shown in Figure 8. Spending increased for most of these therapeutic classes, but spending declines for lipid-lowering drugs, antidepressants, and nonnarcotic pain relievers helped moderate the overall trend.
TOP 10 TREND DRIVERS

Ten therapeutic classes—including diabetes, respiratory, and cancer drugs—were the strongest drivers of trend in 2007. Growth rates for these therapeutic classes are shown in Figure 9.

1. Diabetes therapy
   Plan cost*: 7.0%
   Trend: 12.0%
   Treatments: Type 1 and type 2 diabetes. This class includes insulin products, noninsulin hypoglycemic drugs, blood glucose-monitoring equipment, and other supplies.

Diabetes medications are now the most powerful driver of drug trend. Although utilization growth was relatively moderate in 2007 (2.3%), the unit costs of treatment increased sharply (9.5%). The unit-cost growth reflects price inflation for brand-name products and a shift in treatment mix toward newer, more expensive products.

Utilization growth for insulin products was led by newer products with faster onsets of action or more consistent blood levels, including NovoLog® (a rapid-acting insulin) and Lantus® (a long-acting basal insulin), while utilization of older insulin products continued to decline. Increased utilization of Levemir® (insulin detemir, approved in June 2005) also had a significant impact on 2007 trend, whereas sales growth for Apidra® (insulin glulisine, introduced in 2006) had only a moderate impact. Initial sales of Exubera® (inhaled insulin, approved in January 2006) had a negligible effect on utilization before the product was withdrawn from the market in late 2007. Unit costs for insulin products grew sharply in 2007 (14.5%). Insulin products are available only in brand-name form and do not yet face competition from biogeneric products.

Utilization growth for noninsulin hypoglycemic medications was led by Januvia, the first of a new class of oral medications, dipeptidyl peptidase IV (DPP-IV) inhibitors. Januvia was launched in late 2006. Several other new products also exhibited strong sales growth in this class, including Byetta (a new injectable, approved in April 2005) and two new oral combination drugs, ActoPlus met® (August 2005) and Avandaryl™ (June 2006). Utilization growth for these brands more than offset the sharp decline in Avandia utilization after reports were issued about a potentially higher risk of heart problems among users of the drug.17,18 Although unit costs declined for the many generic products available in this class, price inflation for brand-name products drove strong unit-cost growth overall (8.7%).
2. Respiratory drugs

Plan cost: 5.7%
Trend: 12.2%
Treatments: Asthma, chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension

Spending on respiratory therapies grew rapidly in 2007, led by a rapid increase in unit costs. Utilization of beta-agonist inhalers showed little change year-over-year, but there was a significant shift in product mix as older products were replaced by new brand-name products that use hydrofluoroalkane (HFA) propellants. Oral inhaled steroids showed only moderate growth, but utilization of *Singulair*® and *Spiriva*® continued to increase rapidly. Several specialty drugs for pulmonary hypertension also showed significant growth—*Tracleer*® (an oral treatment), *Revatio* (a new oral treatment, approved in June 2005), and *Ventavis*® (an inhaled treatment).

The rapid unit-cost growth for respiratory drugs (9.6%) was due in part to market shifts toward higher-priced brands, including *Spiriva* and the new single-source beta-agonist inhalers that use HFA propellants. Unit-cost growth was also driven by price inflation for most of the brands in the class. With the transition to the new brand-name HFA inhalers, very few products in the respiratory class are now available in generic form.

3. Cancer and transplant drugs

Plan cost: 3.5%
Trend: 15.5%
Treatments: This class includes antineoplastics, immunosuppressants, antimetabolites, hormone therapies, and molecular target inhibitors that are used in cancer and transplant treatments.

Spending on cancer and transplant drugs has accelerated rapidly over the past few years as new, more targeted therapies are incorporated into cancer treatment protocols. Unit costs continue to be the primary driver of spending growth, as the therapy mix shifts toward newer, more expensive specialty medications that are available only in brand-name form. Unit-cost declines for the few available generic medications (such as methotrexate, tamoxifen, and azathioprine) did little to offset price inflation for many of the leading brands.

Utilization of cancer and transplant treatments increased moderately overall (1.1%), but the therapy mix continued to shift toward newer treatment options. Utilization grew rapidly for some of the brand-name cancer treatments (such as *Gleevec*® and *Revlimid*), immunosuppressant drugs (*CellCept*® and *Prograf*®), and aromatase inhibitors (*Arimidex*® and *Femara*®). Three new oral and highly targeted specialty drugs also had a significant impact on spending growth for cancer treatments in 2007—*Sutent* (January 2006), *Sprycel*® (June 2006), and *Tykerb*® (March 2007). Unlike older cancer drugs, many of the newer agents are administered on a daily basis, rather than intermittently in cycles. The availability of these newer, more targeted drugs is turning cancer chemotherapy into a long-term maintenance treatment.

4. Rheumatological drugs

Plan cost: 3.0%
Trend: 15.6%
Treatments: Rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, and other autoimmune conditions
Spending for rheumatological drugs continued to grow rapidly in 2007, driven primarily by the increased use of these drugs for an expanding range of conditions. Utilization growth was especially strong for two biologics, Enbrel® and Humira®, which are widely used to treat rheumatoid arthritis and other autoimmune disorders. Orencia®, a new infusible biologic treatment for rheumatoid arthritis (approved in February 2006), showed moderate growth in its first full year of sales, but it did not have a significant impact on trend. Utilization growth in the rheumatological class was driven by an expanding set of indications and by increased use of multiple-drug treatments and more frequent treatment intervals.

Unit costs for rheumatological drugs grew rapidly (6.2%) in response to price inflation for the leading brands. First-time generics for Arava® (leflunomide), which were introduced in September 2005, helped moderate spending growth in this class.

5. Seizure drugs
Plan cost: 3.6%
Trend: 12.2%
Treatments: Epilepsy, neuropathic pain, psychiatric disorders

Spending growth for anticonvulsant medications accelerated from 3.2% in 2005 to 12.2% in 2007. Utilization grew rapidly for this class of drugs, driven primarily by an increase in treatment rates for an expanding set of indications. Sales growth was strong for several brand-name products in the class, including Topamax®, Lamictal®, Keppra®, and Lyrica® (approved in December 2004 for the treatment of diabetic peripheral neuropathy). Utilization was essentially unchanged for generic gabapentin (Neurontin®) and clonazepam (Klonopin®), the two most widely used medications in this class, as the therapy mix shifted toward other products. Large unit-cost declines for generic gabapentin and clonazepam helped offset price increases for the leading brand-name drugs.

6. Antiviral drugs
Plan cost: 3.0%
Trend: 14.8%
Treatments: Influenza, hepatitis, herpes, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS)

Spending on antiviral drugs continued to grow at a fast pace in 2007. Spending growth was especially strong for HIV/AIDS therapies, a class of drugs for which generic alternatives are not currently available. Trend was driven strongly by a rapid increase in sales of Atripla®, a new triple-combination treatment for HIV/AIDS (approved in July 2006). Unit costs increased sharply as the therapy mix continued to shift toward higher-cost combination products. Initial sales of Prezista® (approved in June 2006) and Selzentry® (approved in August 2007) had only a moderate effect on trend.

Trend was also robust for miscellaneous antivirals, a class that includes treatments for herpes and influenza. Utilization growth was especially strong for Valtrex® (a treatment for herpes zoster, genital herpes, and cold sores), Baraclude® (for hepatitis B), and Valcyte® (for cytomegalovirus infection). Sales of Tamiflu® declined 5% in 2007, because of a mild flu season and reduced public concern about the possibility of a bird-flu pandemic. Unit costs for these antivirals increased rapidly due to price inflation for the leading brands, but price reductions for generic ribavirin products helped moderate the overall trend.
7. Select neurological drugs

Plan cost: 2.2%
Trend: 17.2%
Treatments: Alzheimer's disease, Parkinson's disease, multiple sclerosis (Copaxone®, Tysabri®)

Spending for neurological drugs to treat Alzheimer’s disease, Parkinson’s disease, and multiple sclerosis increased rapidly in 2007, driven by strong growth in treatment rates and treatment intensity. Utilization grew rapidly for the leading brand-name treatments for Parkinson’s disease (Requip® and Mirapex®) and for the leading treatments for Alzheimer’s disease (Aricept® and Namenda®). Utilization of Tysabri also increased in 2007, following its controlled reintroduction to the market in June 2006. Utilization of Copaxone was essentially unchanged on a year-over-year basis.

Unit costs for this class of neurological drugs also increased rapidly (5.1%). Price inflation drove significant increases in the costs of Alzheimer’s treatments, which are available only in brand-name form. Unit-cost increases for Parkinson’s treatments were more moderate overall.

8. Antipsychotic drugs

Plan cost: 2.2%
Trend: 14.3%
Treatments: Schizophrenia, bipolar disorder, and other psychiatric disorders

Antipsychotic medications showed strong utilization growth in 2007, rebounding from a utilization decline in 2006. This growth was led by increased sales of Seroquel and Abilify®, which more than offset a sales decline for Zyprexa®. Utilization of Risperdal®, another leading product in this class, was essentially unchanged. Initial sales of Invega®, a new treatment for schizophrenia (approved in December 2006), had little impact on trend for the class. The shifts in product mix reflect continuing efforts by clinicians to optimize treatment protocols for psychiatric disorders, based in part on the results of a major national study on the safety and efficacy of antipsychotic medications.28

Unit costs for antipsychotic medications increased sharply in 2007, due to price inflation for the leading brands in the class. Although a few generic alternatives (such as clozapine) are available, single-source brands dominate treatment for this class of psychiatric disorders.

9. Urological drugs

Plan cost: 2.3%
Trend: 12.8%
Treatments: Overactive bladder, erectile dysfunction, benign prostatic hypertrophy (BPH), bladder pain relief

Utilization of drug treatments for overactive bladder and BPH grew rapidly in 2007, stimulated in part by extensive advertising, which has raised consumer awareness of the available treatments for these conditions. Growth was especially strong for two of the leading treatments for BPH (Flomax® and Avodart®). Sales also grew rapidly for Enablex® (a treatment for overactive bladder) and Vesicare® (a treatment for bladder pain and discomfort). Utilization growth for erectile dysfunction treatments was moderate overall.
Unit-cost growth for urologicals was driven by strong price inflation for the brand-name drugs that dominate utilization in this class. The prior-year introduction of two first-time generics—finasteride (Proscar®) and oxybutynin extended-release (Ditropan XL®)—helped moderate unit costs in 2007.

**10. Dermatological drugs**

Plan cost: 2.6%
Trend: 11.0%
Treatments: Acne, psoriasis, skin infections. This class includes topical corticosteroids, anesthetics, and anti-infectives.

Spending growth for dermatological drugs was driven strongly by the increased costs of acne treatments. Utilization growth was slow overall, but price inflation for all of the leading brand-name products, including BenzaClin® and Differin®, drove unit costs upward. Pricing declines for several generic drug treatments, including clindamycin and tretinoin, moderated cost growth overall. Sales growth was especially rapid for two acne treatments, Sotret® and Claravis™.

Treatments for psoriasis and seborrhea also contributed to the strong trend for dermatologicals. Utilization of these treatments was unchanged overall, but there was a significant shift in therapy mix toward Taclonex®, a new treatment that was approved in January 2006. Trend was driven primarily by price inflation for the brand-name drugs, which include two specialty drugs, Raptiva® and Amevive®. Other specialty drugs used for psoriasis are included in the rheumatological class.

**TRENDS MODERATORS**

Three therapeutic classes—lipid-lowering drugs, antidepressants, and nonnarcotic pain relievers—were major decelerators of trend in 2007 (Figure 10).

**1. Lipid-lowering drugs**

Plan cost: 10.8%
Trend: −8.5%
Treatments: Cholesterol and triglyceride management. This class includes statins, fibrates, cholesterol absorption inhibitors, and niacin products.

For many years, lipid-lowering drugs were the leading driver of drug trend. That changed abruptly in 2007 after the generic conversions of two blockbuster statin medications in 2006—Pravachol (pravastatin) and Zocor (simvastatin). In 2007, lipid-lowering drugs became the leading trend reducer, in spite of continued rapid growth in utilization.

Unit costs for lipid-lowering drugs dropped sharply in 2007 (−13.7%), as the cost savings associated with generic pravastatin and simvastatin registered on a full-year basis. A shift in therapy mix toward generic simvastatin accentuated the savings in unit costs.

Utilization of lipid-lowering drugs continued to grow at a rapid pace (5.9%) in 2007—well above the average for prescription drugs as a whole. Utilization declined slightly for Lipitor, the leading statin in the class, as usage shifted toward the new...
generics and to lower-cost brand-name products, such as Crestor® and Vytorin®. Utilization also increased for several other types of lipid-lowering agents, including Zetia® (a cholesterol absorption inhibitor) and TriCor® (a fibrate).

Over the past few years, clinical guidelines have significantly expanded the eligible population for cholesterol-lowering therapy. Recent clinical studies also support more aggressive cholesterol lowering for some patients, which may require the use of multiple agents. Increased prevalence and detection of high cholesterol levels may also be driving growth in this therapeutic class.

### 2. Antidepressant drugs

- **Plan cost:** 5.5%
- **Trend:** –8.4%
- **Treatments:** Depression, anxiety, panic disorder, neuropathic pain

Plan costs for antidepressant medications dropped sharply in 2007, following the generic conversions of two blockbuster brands in 2006—Zoloft (sertraline) and Wellbutrin XL® (bupropion extended release, 300 mg). The full-year effect of these conversions contributed to a major decline in the average unit cost of antidepressant medications (–9.7%). Price reductions for other widely used generics in the class (such as fluoxetine, paroxetine, and citalopram) also contributed strongly to lower unit costs.

Utilization of antidepressants increased slowly in 2007 (1.5%), continuing the moderate pace observed over the past 2 years. Utilization growth had slowed considerably in 2005 in response to concerns about the possible risk of increased suicidality in children and young adults, especially during the first few months of therapy or when dosages are adjusted.

The therapy mix for antidepressants has continued to shift toward the class of “miscellaneous antidepressants,” which includes the serotonin-norepinephrine reuptake inhibitors (SNRIs) and bupropion. Utilization growth in this class was led by a strong increase in sales of Cymbalta®. Utilization grew 5.1% for the miscellaneous antidepressants, compared with only 0.5% for selective serotonin reuptake inhibitors (SSRIs).

Unit costs for the miscellaneous antidepressants increased 3.1%. Price inflation for the leading brands more than offset the savings from the new generic bupropion products. Unit costs declined sharply for the SSRIs (–27.0%), reflecting the impact of generic price competition for almost every drug in the class.

### 3. Nonnarcotic pain relievers

- **Plan cost:** 1.5%
- **Trend:** –16.2%
- **Treatments:** Osteoarthritis, rheumatoid arthritis, tendonitis, bursitis, and other conditions. This therapeutic class includes traditional NSAIDs, such as naproxen and diclofenac, and the COX-2 inhibitor Celebrex.

Spending for nonnarcotic pain relievers declined sharply in 2007, reflecting the full-year impact of the generic conversion of Mobic® (meloxicam) in July 2006. The savings from generic meloxicam, as well as price reductions for the other leading NSAIDs, contributed to a major decline in unit costs for drugs in this class (–13.8%). All of the traditional NSAID products are now available in generic form.

Utilization of nonnarcotic pain relievers declined 2.7% in 2007, reflecting continued concerns about the cardiovascular and gastrointestinal safety of drugs in the class. The utilization decline was observed for almost all of the medications in the class, with the exception of meloxicam.
TREND WATCH: FAST AND SLOW MOVERS

In addition to the top 10 trend drivers, several other therapeutic classes showed especially rapid spending growth in 2007 (Table 4). Although these “fast movers” represent a small percentage of current spending, their rapid growth makes them important trend drivers to monitor and manage closely.

In addition to the three therapeutic classes that showed large spending declines, several other drug classes helped moderate trend in 2007. These “slow movers” exhibited slow spending growth or a gradual spending decline (Table 4).

Table 4. Additional trend drivers with rapid or slow growth in 2007

<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>Narcotic pain relievers</td>
<td>2.9</td>
<td>9.6</td>
<td>5.6</td>
<td>3.8</td>
<td>Increased treatment rates and durations for OxyContin®, oxycodone, and combination products.</td>
</tr>
<tr>
<td>Anticoagulant and antiplatelet</td>
<td>2.7</td>
<td>9.4</td>
<td>2.9</td>
<td>6.4</td>
<td>Rebound in unit costs, following temporary availability of generic Plavix® (clopidogrel) in 2006.</td>
</tr>
<tr>
<td>ADHD</td>
<td>1.8</td>
<td>12.8</td>
<td>5.6</td>
<td>6.8</td>
<td>Rapid increase in treatment rates. Price inflation for single-source extended-release brands, which dominate treatment.</td>
</tr>
<tr>
<td>Miscellaneous agents</td>
<td>0.7</td>
<td>12.9</td>
<td>0.6</td>
<td>12.3</td>
<td>Increased unit costs for select specialty drugs, including Thalomid®, Exjade®, Sensipar®.</td>
</tr>
<tr>
<td>Slow movers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>8.2</td>
<td>2.0</td>
<td>0.6</td>
<td>1.4</td>
<td>Rapid utilization growth for brand-dominated categories—angiotensin receptor blockers (ARBs) and combination products. Offset by unit-cost declines in categories dominated by generics—angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers. New generics for Toprol-XL®, Norvasc®, Lotrel®, Coreg®, Inderal® LA.</td>
</tr>
<tr>
<td>Ulcer and heartburn</td>
<td>7.4</td>
<td>−2.3</td>
<td>0.0</td>
<td>−2.3</td>
<td>Therapy mix shift from single-source brands to lower-cost generic omeprazole. Utilization declines for anemia and interferon treatments. Offset by utilization increases for some growth hormones and vaccines.</td>
</tr>
<tr>
<td>Select biotechnology</td>
<td>3.2</td>
<td>0.7</td>
<td>−1.0</td>
<td>1.7</td>
<td>Price increases for some leading brand-name antibiotics. Offset by price reductions for generic azithromycin and clarithromycin products.</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>3.1</td>
<td>0.7</td>
<td>0.6</td>
<td>0.2</td>
<td>Price inflation for single-source brands. Offset by unit-cost declines associated with generic conversions of Allegra® (fexofenadine) in 2005 and Flonase® (fluticasone) in 2006.</td>
</tr>
<tr>
<td>Allergy</td>
<td>2.8</td>
<td>1.0</td>
<td>0.6</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>
Specialty healthcare

Specialty drugs continue to be a major driver of spending growth in prescription benefit plans. These drugs are used to treat a broad array of complex diseases, including hemophilia, rheumatoid arthritis, psoriasis, cancer, anemia, neutropenia, cystic fibrosis, hepatitis C, and growth hormone deficiency. Several new specialty drugs were introduced in 2007 (Table 2), and several drugs in this class received approval for new or expanded indications (Table 3). Specialty drugs are generally expensive; they typically cost more than $6,000 per year, and in some cases, they may cost more than $250,000 per year. Many specialty drugs are administered by infusion or self-injection, and almost all require special handling or expanded patient support.

THE SPECIALTY CARE DOLLAR

The majority of spending on specialty drugs is concentrated in a small number of therapeutic areas: rheumatoid arthritis and other autoimmune disorders, multiple sclerosis, cancer, growth hormone deficiency, anticoagulation therapy, anemia, and hepatitis C (Figure 11). The remainder of the specialty care dollar is spent on treatments for pulmonary arterial hypertension, osteoporosis, neutropenia, infertility, hemophilia, cystic fibrosis, asthma, and more than a dozen other medical conditions.

Specialty costs continue to grow as a percentage of the total prescription care dollar. For Medco clients, specialty drugs accounted for 11.4% of pharmacy plan spending in 2007, up from 10.4% in 2006.

The costs reported here are for specialty drugs that were purchased under the pharmacy benefit. Combining costs incurred under the pharmacy benefit with those incurred under the medical benefit provides a more complete picture of specialty drug spending. For some plan sponsors, 40% to 70% of specialty drug spending may be billed under the medical benefit. Medications that are often self-administered (such as treatments for multiple sclerosis and hepatitis C) are more likely to be billed under the pharmacy plan, whereas infused products (such as treatments for cancer and immune disorders) are more likely to be billed under the medical plan. 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 TREND

Pharmacy spending for specialty drugs continues to grow rapidly, although the rate of growth has slowed in recent years. Specialty spending increased 12.3% in 2007, a significant decline from the 16.1% growth rate in 2006. Price inflation for brand-name specialty drugs was the largest driver of spending growth.

Utilization of specialty drugs increased 3.9% in 2007, exceeding the average utilization growth of 1.6% for prescription drugs as a whole. This growth was driven by several factors: introduction of new specialty medications, increased use of specialty products for current and new indications, and wider use of multiple-drug therapy for some conditions. Some of the utilization growth may also be a by-product of clients’ efforts to shift some of the billing of specialty drugs from the medical plan to the pharmacy plan.
Unit costs for specialty drugs increased 8.4% during 2007. Price inflation for many of the specialty products and shifts toward newer, higher-cost options in some therapeutic categories were the primary drivers of this growth. Therapy mix changes are limited for specialty drugs because few therapeutic alternatives exist for many of these drugs and very few generic options are available.

**SPECIALTY GROWTH DRIVERS**

The growth in pharmacy spending for specialty drugs was concentrated in a small number of therapeutic areas (Figure 12). Spending increases were highest for drugs used to treat rheumatoid arthritis and other autoimmune disorders, cancer, multiple sclerosis, deep vein thrombosis, pulmonary arterial hypertension, and growth hormone deficiency.

**Top trend drivers**

Growth rates for the top drivers of specialty trend are shown in Figure 13. For some specialty drug classes, such as autoimmune disorders and pulmonary arterial hypertension, utilization growth was the primary contributor to trend. For other classes, such as cancer and multiple sclerosis, increased unit costs were the primary driver of trend.

**Fast movers**

Several “fast movers,” drug classes that exhibit exceptionally rapid spending growth, also contributed to specialty trend in 2007. Each fast-mover class contained a single specialty drug that showed rapid growth in utilization: Sensipar® (for hyperparathyroidism), HP Acthar® Gel (an adrenocorticotropic hormone), and Exjade® (for iron chelation therapy).
**Trend moderators**
Two specialty drug classes—anemia and hepatitis C—showed significant spending declines in 2007, moderating the overall growth rate for this category (Figure 13). Utilization of anemia treatments declined following the release of an FDA public health advisory on these products (Aranesp, Epogen, and Procrit).

**SPECIALTY DRUGS: A LEADING DRIVER OF TREND**

The spending growth for specialty drugs accounted for 34.2% of the total growth in drug spending in 2007. Specialty drugs are now the largest contributor to drug trend. They contributed more to spending growth than diabetes drugs, CNS drugs, or any other category of plan spending.

Specialty drugs were a significant component of trend for several of the top 10 trend drivers, including respiratory, cancer, and rheumatological drugs (Figure 14).

- **Respiratory.** A significant portion of the spending growth was driven by specialty drugs used to treat allergic asthma (Xolair®) and pulmonary arterial hypertension (such as Revatio, Ventavis, and Tracleer).
- **Cancer and transplant.** Trend was driven strongly by price inflation for brand-name therapies and a shift in therapy mix toward newer, more targeted therapies.
- **Rheumatological.** Spending growth was dominated by specialty drugs (such as Enbrel and Humira) that are used to treat rheumatoid arthritis and other autoimmune conditions.
- **Select neurological.** Specialty treatments for multiple sclerosis (Copaxone, Tysabri) were a significant contributor to trend in this class.

**Figure 14. Contribution of specialty drugs to the top 10 trend drivers**

Source: Medco data

The figure shows the relative contribution of specialty drugs and nonspecialty drugs to the top 10 trend drivers in 2007. The bars represent the percent contribution of each therapeutic class to the total increase in plan cost. The net contribution to trend (combining specialty and nonspecialty) is the same as that illustrated in Figure 8.

**Medicare trend**

Introduction of the Medicare Part D prescription drug benefit in January 2006 marked the beginning of a new era in government-subsidized benefits for the elderly and disabled. The new benefit has had a profound impact on the pharmacy benefit options available to individuals who are eligible for Medicare. Plan sponsors responded to the new federal initiative by restructuring existing benefit plans and developing a wide array of new plan options for enrollees:

- Health plans created prescription drug plans (PDPs) based on the standard benefit defined in Medicare Part D, as well as more comprehensive Medicare Advantage prescription drug (MA-PD) plans under Medicare Part C.
- Employers, government plans, and labor groups pursued several options for retooling their benefit plans. Some remained a primary payer (with the option to receive federal subsidies) or offered secondary coverage to Medicare Part D. Others established a PDP for eligible retirees or provided “enhanced” coverage through an outside PDP.
The impact of these changes on payer costs and drug utilization is of great interest to policy makers and plan sponsors. This year provides the first opportunity to assess spending growth for Medicare plans, since we now have two full years’ data on plan costs and drug utilization for enrollees in these plans.

**THE MEDICARE DOLLAR**

The top five categories of prescription drug spending for Medicare enrollees in 2007 were cardiovascular (30.7%), CNS (19.6%), gastroenterology (9.8%), endocrine and diabetes (8.4%), and respiratory (7.5%). The extensive use of cardiovascular medications is not surprising, given the demographic composition of these plans. Enrollees in Medicare plans are predominantly age 65 or older, although these plans also include disabled people under age 65 who are eligible for Medicare benefits.

A more detailed picture of prescription drug spending under Medicare is provided in Figure 15. The top two therapeutic classes (lipid-lowering and antihypertensive drugs) accounted for more than 25% of plan spending in 2007. Treatments for acid peptic disorders, diabetes, and respiratory conditions were also leading contributors to plan spending.

**MEDICARE SPENDING GROWTH**

Average plan costs for Medicare enrollees were unchanged in 2007 (compared with the average plan costs for 2006). Drug trend for these plans was 0.0%, well below the 2.0% average for benefit plans as a whole.

The flat overall trend for Medicare plans was the net result of offsetting changes in different segments of the Medicare market. Plan costs for employer-primary coverage grew 1.6%—close to the average for benefit plans as a whole. Trend for these plans was moderated by a small increase in average retiree drug subsidy (RDS) levels. Plan costs for PDP and MA-PD enrollees declined slightly (–2.8%), because of a net reduction in low-income-subsidy enrollees in some of these plans.

Drug utilization by Medicare enrollees increased 4.3% in 2007, faster than the average utilization growth for benefit plans as a whole (1.6%). Utilization growth was similar across the different types of Medicare plans. The rapid utilization growth was offset by a sharp decline in unit costs (–4.3%), which was driven by increased use of generics and mail-service dispensing by enrollees in these plans. Changes in average subsidy levels and plan demographics also contributed to the reductions in unit cost.

---

1. The analysis of Medicare trend is based on 2 years’ data on pharmaceutical spending by enrollees in Medicare Part D and employer-primary plans in 2007. These drug classes fall within broad therapeutic categories such as cardiovascular, CNS, and gastroenterology. For example, lipid-lowering drugs (13.3%), antihypertensives (12.0%), and anticoagulant/antiplatelet drugs (4.5%) comprise most of the spending in the cardiovascular category (30.7% of total cost); the small remaining drug classes are included in “Other.”

2. The reduction in low-income-subsidy enrollees between 2006 and 2007 had a significant one-time impact on Medicare trend. These enrollees tend to have higher-than-average plan costs and low member cost share, so the shift in plan demographics reduced unit costs on a year-over-year basis. After adjusting for this shift, the underlying trend for Medicare enrollees was 4.5%. This may provide a better benchmark for gauging Medicare trend on a going-forward basis.
**MEDICARE TREND DRIVERS**

The therapeutic classes with the largest impact on Medicare trend are shown in Figure 16. Plan costs increased most rapidly for cancer and transplant, diabetes, and respiratory medications. Plan costs declined sharply for lipid-lowering, antipsychotic, and antidepressant medications.

For several of the top trend drivers, such as cancer and respiratory drugs, Medicare trend was driven primarily by increases in unit costs (Figure 17). These treatment areas are dominated by the use of single-source brand-name drugs, which have relatively high rates of price inflation. For other therapeutic classes, spending growth was driven primarily by increases in drug utilization. Treatment rates grew rapidly for select neurological drugs (for Alzheimer’s and Parkinson’s diseases) and urological drugs.

Utilization also increased rapidly for lipid-lowering drugs (11.0%), but this growth was more than offset by a sharp reduction in unit costs associated with two newly available generic drugs, simvastatin and pravastatin. Generic drug use also contributed to a large spending decline for antidepressant drugs. Many commonly used antidepressants are now available in generic form, and price competition among manufacturers continues to reduce the average costs of treatment.

Figure 16. Top therapeutic classes contributing to Medicare drug trend in 2007
Source: Medco data

Note: The figure shows the contribution of each therapeutic class to the overall Medicare trend in 2007. Therapeutic classes are rank-ordered from the largest positive contributor to trend (at the top) to the largest negative contributor to trend (at the bottom).

<table>
<thead>
<tr>
<th>PERCENT CONTRIBUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer &amp; transplant</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Respiratory</td>
</tr>
<tr>
<td>Select neurological</td>
</tr>
<tr>
<td>Antihypertensives</td>
</tr>
<tr>
<td>Urological</td>
</tr>
<tr>
<td>Anticoagulant &amp; antiplatelet</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Lipid-lowering</td>
</tr>
</tbody>
</table>

Figure 17. Spending growth for the top drivers of Medicare trend in 2007
Source: Medco data

Note: Year-over-year changes are shown for plan cost (drug trend), utilization (days per eligible), and unit cost (cost per day). Spending growth factors multiply to yield total trend, so utilization growth and unit-cost growth may not be additive.
Demographics of trend

Prescription drug use varies markedly by age group, geographic region, and many other sociodemographic factors. Some of this variation is associated with differences in disease prevalence, comorbidity rates, treatment-seeking behavior, and clinical practice.

**AGE GROUP VARIATIONS**

In 2007, drug trend was highest for children (age 0 to 19) and seniors (age 65 and older), even though their baseline levels of utilization were very different (Figure 18). Prescription drug spending grew at faster-than-average rates for both of these age groups, while spending growth for the other age groups was relatively slow. Although children showed the lowest level of prescription drug utilization, plan spending for their drugs grew at a rapid pace in 2007. Seniors showed the highest level of spending per member—almost three times the average for the population as a whole—and they also showed the highest rate of spending growth.

Figure 18. Drug spending and trend rates by age group in 2007
Source: Medco data

Note: The Y axis shows the relative level of plan cost and trend for each age group compared with the average level for the plan population as a whole. A value of 1.0 indicates the average level for the plan population. Values above 1.0 indicate above-average levels. For example, plan costs for seniors were almost three times the population average, and drug trend for seniors was more than double the rate for the population as a whole. Trend is the percent change in plan cost on a year-over-year basis; plan costs are per member per month (PMPM).
Patterns of medication use also varied widely by age group, reflecting the different medical conditions that predominate in each group (Figure 19). For children, spending was highest for medications for respiratory conditions (including asthma and allergies), neurological and behavioral disorders, and infections. For younger adults (age 20 to 49), spending was highest for CNS drugs, especially antidepressants and anticonvulsants. For seniors (age 65 and older), spending was highest for drugs for cardiovascular conditions, acid peptic disorders, and diabetes.

Figure 19. Drug spending by therapeutic category and age group
Source: Medco data

Note: For the top seven categories of spending in 2007, 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 utilization rates varied widely across the United States. In 2007, utilization levels were more than 46% higher in the 10 states that had the highest utilization per member, compared with the 10 states that had the lowest utilization (Figure 20). These regional variations reflect differences in demographics, benefit plan mix, disease prevalence, care-seeking behavior, physician prescribing, and other factors.

In the 10 states with the highest drug utilization rates, treatment rates were especially high for antihypertensive, lipid-lowering, and diabetes medications. These states also tend to have smoking and obesity rates above the national average. Smoking rates exceed the national average in eight of these states, and obesity rates are above the national average in another eight of these states (Figure 20). Tobacco use is associated with higher rates of cardiovascular disease, and obesity is associated with higher rates of diabetes and cardiovascular disease, which may account for some of the variation in treatment rates observed in different states.41,42

**Figure 20. Drug utilization by state in 2007**

Source: Medco data

<table>
<thead>
<tr>
<th>LEVEL OF Utilization</th>
<th>STATES</th>
<th>AVERAGE THERAPY DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest</td>
<td>MI, DE, KY, OH, IN, ME, OK, AL, TN, VT</td>
<td>570-749</td>
</tr>
<tr>
<td>High</td>
<td>WV, PA, SC, NH, NV, LA, AR, VA, IL, MS</td>
<td>487-559</td>
</tr>
<tr>
<td>Medium</td>
<td>FL, NC, MO, HI, MA, SD, NM, KS, AK, TX</td>
<td>430-480</td>
</tr>
<tr>
<td>Low</td>
<td>CA, IA, NJ, WY, WI, CT, ID, MD, MT, RI</td>
<td>392-428</td>
</tr>
<tr>
<td>Lowest</td>
<td>UT, AZ, NY, OR, CO, WA, GA, MN, ND, NE</td>
<td>327-390</td>
</tr>
</tbody>
</table>

Note: The states are grouped into five quintiles from highest to lowest utilization. The average number of therapy days per member per year (PMPY) was calculated for each state. The table 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 smoking and obesity rates above the national average.
A LOOK AT THE NEXT THREE YEARS

PROJECTING THE FUTURE
Looking ahead to the next 3 years, you will be able to foresee:

- **The key developments that will drive utilization and cost.**
  New specialty drugs for common and rare conditions will be leading drivers of future drug trend. New indications and combination therapies will also fuel future growth. A continuing wave of first-time generics will reduce price inflation sharply.

- **How to adjust your plan to keep pace with projected change.**
  Plan designs and coverage policies can be adjusted for future events that are already in view—new specialty drugs, new biomarker tests, and new generics for blockbuster brands.

### Trend projections

Over the next few years, drug trend will be shaped by moderate increases in treatment rates, high price inflation for branded drugs, and low unit-cost growth for many new and existing first-time generics. Advances in pharmacogenomics and specialty drug development will produce many new, high-cost therapies for the treatment of various cancers, immune-mediated disorders, central nervous system (CNS) disorders, enzyme-deficiency disorders, and other rare diseases. All of this will occur against a backdrop of nonspecialty drug development, aggressive pharmaceutical marketing, and ongoing patent extension activities.

This report identifies 160 new drugs in the pipeline and 25 first-time generics over the next 3 years. About one-third of the pipeline drugs are likely to be specialty drugs. Also, as many as 25 of the pipeline drugs will be used to treat rare diseases. The drugs included in this report may be of interest to payers for a number of reasons, including:

- Many of the new drugs are expected to be costly and are being studied only for certain narrow uses or in certain small populations. Some may use biomarkers to identify potential patients who will or will not benefit.
- They may represent more expensive treatment options that might not confer a clear advantage over existing drugs.
- They may be intended for uses that do not qualify under the current benefit.
- They may be in categories for which generic options are or soon will be available.

This section begins with an overview of what lies ahead—pipeline drugs, new indications, new over-the-counter (OTC) products, first-time generics, and follow-on biologics—and their potential impact on trend. These developments continue to present challenges and opportunities for innovative plan design and coverage management.
TREND FORECAST: THE NEXT 3 YEARS

Based on existing plan designs and coverage provisions, Medco expects the average wholesale price (AWP) drug trend for plan sponsors to increase between 6% and 9% annually over the next 3 years (Table 1). These trend projections are computed at the AWP level, unadjusted for changes in discounts, rebates, cost sharing, and federal Medicare subsidies. Measures of actual plan performance, such as net cost trend, will likely be lower, perhaps by several percentage points, than these projections.

Table 1. Drug trend projection for 2008–2010*

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utilization increase</td>
<td>2% to 3%</td>
<td>2% to 3%</td>
<td>2% to 3%</td>
</tr>
<tr>
<td>Price and mix increase</td>
<td>4% to 6%</td>
<td>4% to 6%</td>
<td>4% to 6%</td>
</tr>
<tr>
<td>Annual total</td>
<td>6% to 9%</td>
<td>6% to 9%</td>
<td>6% to 9%</td>
</tr>
</tbody>
</table>

*Projected change in drug spending on an average wholesale price (AWP) 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 below the lower limit of this range.

AWP-based unit cost, mostly driven by price inflation, is expected to exceed utilization growth as a trend component over the next 3 years. Price inflation and mix are expected to account for about 70% of trend in this forecast period. The major brands are driving AWP-based unit-cost growth. In 2007, the average price inflation for the top 50 brands was high—about 8%, while price inflation among generics was less than 1%.

Net unit costs (after discounting, rebates, and cost sharing) are likely to grow at or slightly below the rate of utilization over the next 3 years because of the number of new generics expected to enter the market and increased emphasis on plan design incentives that encourage generic utilization.

FORECASTING TREND

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

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

The 2008–2010 drug trend forecast is based on utilization and cost data for a 3-year historical period (2005–2007) for a large set of clients with integrated retail and mail-order benefits. The average monthly enrollment in the data sample was 38 million members. This year’s projections include members who 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
- 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 criteria

Over the next 3 years, more than 80% of drug trend will be driven by drugs in 7 of the 16 broad chapters in the Preferred Prescriptions® Formulary (Figure 1). The cardiovascular and CNS drug categories will account for more than half of the spending growth. Detailed projections at the AWP level for the top therapeutic categories are provided later in this section, beginning on page 42.

Within these broad categories, nine specific drug classes—including lipid-lowering drugs, diabetes treatments, antidepressants, antihypertensives, and drugs for cancer—will account for almost 60% of spending growth over the next 3 years (Figure 2).

Figure 1. Top therapeutic chapters contributing to projected drug trend (2008–2010)
Source: Medco projection

Figure 2. Top therapeutic classes contributing to projected drug trend (2008–2010)
Source: Medco projection

Note: The figure shows the seven therapeutic chapters that are likely to drive the majority of spending growth between 2008 and 2010. Data are expressed as a percentage of the total projected increase in AWP-based plan cost.

Note: The figure shows the nine therapeutic classes that are likely to drive the majority of spending growth between 2008 and 2010. Data are expressed as a percentage of the total projected increase in AWP-based plan cost.
Market projections

**NATIONAL DRUG TREND**

The Centers for Medicare & Medicaid Services (CMS) estimates that national healthcare spending grew by 6.7% in 2006.\(^1\) Prescription drug spending grew at an accelerated rate of 8.5%—above the all-time low of 5.8% in 2005, but well below the average 13.4% increase that occurred between 1995 and 2004. According to CMS, among the contributors to the more rapid growth in drug expenditures nationally during 2006 were full implementation of the Medicare Part D program, which resulted in increased drug use, and the increased availability and use of specialty drugs. CMS estimates that national drug spending grew 6.7% in 2007.\(^2\)

CMS predicts that the average annual increase in national drug expenditures over the next 10 years will be 8.4%.\(^2\) This increase will be fairly evenly split between price inflation and utilization increases. Beginning in 2010, prescription drugs will emerge as the fastest-growing major segment of national healthcare expenditures.\(^2\)

**DRUG PIPELINE**

The world’s top pharmaceutical companies have 1,752 drugs in clinical development in the top ten therapeutic categories.\(^3\) Drugs for the treatment of cancer continue to be the largest area of new drug development (Figure 3). Many of the new drugs, especially those in the oncology area, will be more targeted, long-term therapies that may use genetically based information or tumor biomarkers to identify patients who should receive these drugs.

Approximately 475 of the drugs in clinical development are in Phase III clinical trials for marketing in the United States, and almost 800 drugs are in Phase II clinical trials.\(^4\) About half of the products in Phase III development are new molecular entities (NMEs); the rest are new combination products or drugs with new dosage forms or routes of administration.

Many of the drugs in development will be used to treat orphan conditions—rare diseases such as amyloidosis, Huntington’s disease, hereditary angioedema, chronic lymphocytic leukemia, and idiopathic pulmonary fibrosis. Since passage of the Orphan Drug Act about 25 years ago, over 315 orphan drugs or orphan indications for existing drugs have been approved. In 2007, almost one-third of the NME approvals were for orphan drugs. In 2006 and 2005, 17% and 33% of NME approvals, respectively, were for orphan drugs. These drugs are intended for use in underserved patient populations and thus may be treated more favorably by the FDA and ushered more quickly through the review process.
Many potential blockbuster drugs can be expected to come to market in the next few years, including new specialty and nonspecialty medications for cancer, CNS disorders, diabetes, immunological diseases, and cardiovascular disorders. Some of these drugs are likely to reach annual sales in excess of $1 billion. Possible future blockbusters include continuous erythropoietin receptor activator, prasugrel, rivaroxaban, dabigatran, denosumab, ustekinumab, golimumab, tocilizumab, and exenatide (long-acting formulation).

New drugs
As in 2006, the FDA approved relatively few new drugs in 2007—16 NMEs and 7 therapeutic biologics, blood products, or vaccines. The 16 NMEs represent 1 fewer than the 20-year low of 17 NMEs approved in 2002.

In 2007, approvable and nonapprovable letters were issued in response to a large number of new drug applications (NDAs). Nonapprovable letters were issued in 2007 for rimonabant, etoricoxib, lumiracoxib, and motexafin. Approvable letters were issued for vildagliptin, human papilloma virus vaccine, indiplon, bazedoxifene, and dalbavancin. It appears that the FDA has become more stringent regarding drug safety and is increasingly demanding additional data and studies from manufacturers before approving new drugs.

As of January 2008, there were about 40 new drugs with user-fee goals for FDA action in 2008. The number of drugs at the point of NDA submission, combined with those with approvable letters, could mean a rebound in new drug approvals for 2008. Across all the drugs in the pipeline, an average of 25 to 30 new drug approvals is still possible in each of the next 3 years, including both NMEs and therapeutic biologics.

New indications
Expanding the labeled indications for currently approved drugs continues to be a focus for product development, especially for specialty drugs. Gaining a new indication provides a means of expanding the current market or developing a completely 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. Some of these new indications, if approved, could have a significant impact on utilization growth and spending growth over the next several years. Approvals for new indications are being sought for Atacand® (treatment of diabetic retinopathy), Avodart® (prevention of prostate cancer), Cymbalta® (treatment of fibromyalgia), Diovan® plus Starlix® (prevention of diabetes), and Nexavar® (treatment of breast cancer), to name just a few. These new indications represent significant new user populations for these brand-name drugs that could contribute to rising utilization.
New dosage forms and combination products

New extended-release dosage forms, combination products, and drug-delivery systems have always been a major focus of product development, and they represent a high percentage of pending NDAs. Some significant examples of these types of products include lamotrigine extended release, levetiracetam extended release, sumatriptan/naproxen, gabapentin extended release, ropinirole extended release, naproxen/esomeprazole, and choline fenofibrate/rosvustatin. Many of these new products will compete with generic drugs that are already available or that are likely to be introduced soon.
## First-Time Generics

Drugs with total U.S. sales of nearly $24 billion could lose patent protection over the next 3 years, expanding the potential market for lower-cost generics. This 3-year period of first-time generics could be eclipsed by more than $42 billion in new first-time generics in 2011 and 2012. Thus, a total of more than $66 billion in current drug spending could be affected by generic competition over the next 5 years.

Most of the anticipated patent expirations and first-time generics over the next 3 years are shown in Table 3. The number of first-time generics could increase even more if manufacturers continue to challenge patents and launch new generics on an at-risk basis (before patent expiration), as happened several times in 2007, or if manufacturers secure unexpectedly favorable outcomes in ongoing patent litigation.

Table 3. Some potential patent expirations for 2008–2010

Sources: Electronic Orange Book; IMS (retail sales)

<table>
<thead>
<tr>
<th>Possible patent expiration</th>
<th>Brand name (generic name), manufacturer</th>
<th>Uses</th>
<th>2007 U.S. retail sales ($M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>Risperdal® (risperidone), Janssen</td>
<td>Schizophrenia</td>
<td>$2,000</td>
</tr>
<tr>
<td></td>
<td>Lamictal® tablets (lamotrigine), GlaxoSmithKline</td>
<td>Seizure disorders, bipolar disorder</td>
<td>$1,937</td>
</tr>
<tr>
<td></td>
<td>Fosamax® (alendronate), Merck</td>
<td>Osteoporosis</td>
<td>$1,450</td>
</tr>
<tr>
<td></td>
<td>Imitrex® (sumatriptan tablets), GlaxoSmithKline</td>
<td>Migraine headache</td>
<td>$1,300</td>
</tr>
<tr>
<td></td>
<td>Keppra® (levetiracetam), UCB</td>
<td>Seizure disorders</td>
<td>$783</td>
</tr>
<tr>
<td></td>
<td>Depakote® (divalproex), Abbott</td>
<td>Seizure disorders, bipolar disorder</td>
<td>$678</td>
</tr>
<tr>
<td></td>
<td>Requip® (ropinirole), GlaxoSmithKline</td>
<td>Parkinson’s disease</td>
<td>$414</td>
</tr>
<tr>
<td></td>
<td>Paxil CR® (paroxetine controlled release), GlaxoSmithKline</td>
<td>Depression, social anxiety disorder, panic disorder</td>
<td>$307</td>
</tr>
<tr>
<td></td>
<td>Donovex® (calcipotriene), Warner Chilcott</td>
<td>Psoriasis</td>
<td>$162</td>
</tr>
<tr>
<td></td>
<td>Serewent® Diskus® (salmeterol), GlaxoSmithKline</td>
<td>Asthma, COPD</td>
<td>$109</td>
</tr>
<tr>
<td></td>
<td>Tegretol®-XR (carbamazepine extended release), Novartis</td>
<td>Seizure disorders</td>
<td>$85</td>
</tr>
<tr>
<td>2009</td>
<td>Prevacid® (lansoprazole), Novartis</td>
<td>Ulcers, GERD</td>
<td>$3,125</td>
</tr>
<tr>
<td></td>
<td>Topamax® (topiramate), Ortho-McNeil</td>
<td>Seizure disorders, migraine headache</td>
<td>$2,000</td>
</tr>
<tr>
<td></td>
<td>Valtrex® (valacyclovir), GlaxoSmithKline</td>
<td>Viral infections</td>
<td>$1,651</td>
</tr>
<tr>
<td></td>
<td>AcipHex® tablets (rabeprazole), Eisai</td>
<td>Ulcers, GERD</td>
<td>$1,230</td>
</tr>
<tr>
<td></td>
<td>Ambien CR® (zolpidem extended release), Sanofi-Aventis</td>
<td>Insomnia</td>
<td>$980</td>
</tr>
<tr>
<td></td>
<td>Clarinex® (desloratadine), Schering</td>
<td>Allergies</td>
<td>$350</td>
</tr>
<tr>
<td></td>
<td>Casodex® (bicalutamide), AstraZeneca</td>
<td>Prostate cancer</td>
<td>$220</td>
</tr>
<tr>
<td></td>
<td>Prandin® (repaglinide), Novo Nordisk</td>
<td>Type 2 diabetes</td>
<td>$131</td>
</tr>
<tr>
<td></td>
<td>Sonata® ( zaleplon), King</td>
<td>Insomnia</td>
<td>$92</td>
</tr>
<tr>
<td>2010</td>
<td>Flomax® (tamsulosin), Boehringer Ingelheim</td>
<td>Benign prostatic hypertrophy</td>
<td>$1,062</td>
</tr>
<tr>
<td></td>
<td>Cozaar® (losartan), Merck</td>
<td>High blood pressure</td>
<td>$693</td>
</tr>
<tr>
<td></td>
<td>Arimidex® (anastrozole), AstraZeneca</td>
<td>Breast cancer</td>
<td>$549</td>
</tr>
<tr>
<td></td>
<td>Hyzaar® (losartan/hydrochlorothiazide), Merck</td>
<td>High blood pressure</td>
<td>$515</td>
</tr>
<tr>
<td></td>
<td>Accolate® (zafirlukast), AstraZeneca</td>
<td>Asthma</td>
<td>$47</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.
The launch of a large number of new, high-volume generics over the next 3 years will help drive down unit-cost growth in several therapeutic categories as utilization shifts to the low-cost generic options. However, the introduction of new brand-name drugs, especially high-priced biotech and specialty drugs, will 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 2009 or 2010. The savings from first-time generics for Keppra® (levetiracetam) and Lamictal® (lamotrigine) could be reduced by extended-release formulations of these drugs that are now in the pipeline.

**FOLLOW-ON BIOLOGICS (BIOSIMILARS)**

Protein-based drugs, many of which are produced using recombinant DNA technology, are playing an increasingly important role in therapy for many conditions. In fact, since the first recombinant human insulin product entered the market in 1982, over 100 different recombinant protein-based drug products have been approved. Another 400 biologics and protein-based drugs are in various stages of clinical development. In 2006, national spending on protein-based and biologic drugs amounted to about $54 billion, 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 generic competitors in this category has contributed to the rapid growth in spending for these drugs.

Patents on some older protein-based drugs have expired or will expire over the next few years. Thus, the availability of generic versions of these drugs—most appropriately referred to as follow-on biologics or biosimilars—could reduce medication costs significantly. In fact, even at only modestly discounted prices, such as 15% or 20% off the price of the brand, the aggregate savings from follow-on biologics could be substantial because these drugs can cost between $15,000 and $150,000 per patient per year.

**Interchangeability**

Several significant barriers exist to the market availability of follow-on biologics. One of them—a key issue facing the industry, the FDA, and payers—is whether follow-on biologics can be deemed **interchangeable** with reference drugs, or are only **biosimilar** to them. Unlike traditional medications, biologic medications are derived from living matter and are generally made up of large, complex proteins. These large protein molecules arrange themselves in complicated three-dimensional structures that may undergo biochemical modifications, and they form aggregates with other similar protein molecules in solution. Even very small variations in the manufacturing processes for biologics will result in changes in molecular structure, aggregation potential, or other biochemical properties that affect drug action and, most important, immunogenicity. Therefore, it is difficult for scientists to compare follow-on biologics with their reference products, and sophisticated technologies to determine comparability must be developed.

**Regulatory pathways**

Another major barrier to the market availability of follow-on biologics 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 of 1944, which does not contain any provisions for approval of biogeneric versions. The U.S. Senate and House of Representatives are both reviewing legislation that would permit applications for licensure of biosimilar biologic products. The pending bills specify how biosimilarity or interchangeability with a reference product would be tested and documented. They also establish periods of market exclusivity for the original biologic product and for the first approved biogeneric version of the reference product.

**Patent protection**

Whereas patents on traditional drugs are often the only obstacles to the introduction of generic versions of these agents, patents on the manufacturing processes for certain biologics may further protect them from being “copied” by biogeneric manufacturers. In the world of recombinant protein-based drugs, it is often said that “the manufacturing process is the product.”
Patents have already expired for about $15 billion worth of biologics in the global market (including unaltered human insulins, human growth hormones, and nonpegylated alpha interferons), and these drugs are expected to be early targets for biosimilars. However, many other biologics are still patent-protected in the United States until at least 2014—such as epoetin alfa (Epogen®, Procrit®), etanercept (Enbrel®), and many other high-value monoclonal antibody drugs.

The future of biosimilars
In spite of the current obstacles, creation of a route to market for biosimilars appears to be only a few years away. In Europe, where biosimilars are not considered interchangeable with reference brand products, biosimilars have already been approved for human growth hormone and human erythropoietin. The European Medicines Agency has also set standards for biosimilars involving human insulin, granulocyte colony-stimulating factor agents, and interferon alfa.

Estimates of the potential savings from follow-on biologics depend on assumptions about future patent challenges and expirations, pricing strategies for the brand and follow-on versions, development of new analytic technology to determine comparability, acceptance rates, and the number of generic manufacturers with approved biosimilar drugs. One recent report estimated savings of between $67 and $108 billion over a 10-year period and $236 to $378 billion over the next 20 years. As soon as they become available, follow-on biologics will begin to offer plan sponsors and patients an opportunity to reduce their costs for highly expensive biologic therapies.

**RX-TO-OTC SWITCHES**

The conversion of prescription drugs to OTC status is a trend that will continue. OTC versions were approved for several products in 2007, including Zyrtec® (cetirizine) and Alli®, an OTC version of the weight-loss product Xenical® (orlistat). OTC conversion of an additional non-sedating antihistamine, Clarinex® (desloratadine), is expected in 2009. Novartis has acquired the rights to market OTC versions of Prevacid® (lansoprazole) when the 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® is also expected by 2010.

**KEY THERAPEUTIC DEVELOPMENTS**

For the first time, oncology is one of the top seven categories that will drive spending growth over the next 3 years (Figure 1). Specialty and orphan drugs for the treatment of cancer, as well as non–cancer-related specialty drugs, will become increasingly important trend drivers over the next 3 years. Detailed forecasts of developments in these different therapeutic areas are provided in the following sections of this report.
Cardiovascular agents

Contribution to plan spending (2007): 22.4%
Projected contribution to trend (2008 to 2010): 28%

Projected trend

Table 4. Drug trend projection for cardiovascular 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>2008</td>
<td>5% to 6%</td>
<td>1% to 2%</td>
<td>9% to 11%</td>
</tr>
<tr>
<td>2009</td>
<td>1% to 2%</td>
<td>6% to 7%</td>
<td>7% to 9%</td>
</tr>
<tr>
<td>2010</td>
<td>2% to 3%</td>
<td>6% to 7%</td>
<td>8% to 10%</td>
</tr>
</tbody>
</table>

*T trend predictions

Key developments that are likely to shape drug trend in the cardiovascular category over the next 3 years:
- Expansion of guidelines-based treatment for patients with cardiovascular disorders, such as hypertension, congestive heart failure, stroke, peripheral vascular disease, and ischemic heart disease
- Higher use of preventive therapies such as cholesterol-lowering drugs and drugs that increase high-density lipoprotein (HDL) levels
- Increased use of combination therapies to achieve lower and more aggressive treatment goals for cardiovascular conditions
- New anticoagulants that will not require intensive monitoring
- More potent antiplatelet drugs for treating and preventing arterial thrombotic events and reducing the risk of heart attack and stroke
- Continued unit-cost savings resulting from generic availability of beta-blockers, statins, angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers

Trend drivers: Cholesterol management drugs, antiplatelet and anticoagulant drugs, angiotensin II receptor blockers (ARBs)
Trend moderators: Calcium channel blockers, beta-blockers

Although significant progress has been made in managing cardiovascular disease, as evidenced by the 33% decline in age-adjusted cardiovascular disease in the U.S. population between 1990 and 2004, cardiovascular disease remains a leading cause of death and disability in the United States. In 2006, healthcare spending and lost productivity attributed to cardiovascular disease is estimated to have exceeded $400 billion. Approximately one-third of adult Americans (about 71.3 million) have at least one type of cardiovascular disorder. Among the most common types are hypertension (65 million), coronary heart disease (13.2 million), prior stroke (5.5 million), and heart failure (5 million).13

About 36 million Americans, including almost all patients with diabetes, are candidates for cholesterol-lowering therapies, and not all these patients are receiving treatment. Widespread adoption of statin therapy has likely contributed to early achievement of the Healthy People 2010 objective of a mean serum cholesterol level among adults of less than 200 mg/dL, but further progress is needed. Excessively high serum cholesterol values (240 mg/dL or higher) still affect 16% of adults age 20 or older and about 19% of adults age 40 to 59. Furthermore, several million American men and women
have HDL levels that are too low. Epidemiologic data indicate that low HDL values are a significant risk factor for serious cardiovascular events. Although direct evidence for a cardiovascular benefit from raising HDL levels with drug therapy is still lacking, the next crop of cholesterol management therapies is aimed at lowering low-density lipoprotein (LDL) levels while simultaneously increasing HDL levels.

## LIPID-LOWERING AND HDL-RAISING DRUGS

AWP spending on statins, statin combinations, and other cholesterol-lowering drugs is expected to grow at approximately 8% to 12% per year over the next 3 years. Generic availability in the category will continue to help moderate unit costs, but rising utilization and new combination products aimed at affecting both LDL and HDL levels will counter some of the savings from generics.

### Treatment guidelines

Utilization of statins will continue to grow because clinical guidelines have expanded the treatment-eligible population to include patients with normal cholesterol levels who have risk factors for heart disease. Clinical studies published in the last few years provide evidence of greater reductions in morbidity and mortality with more aggressive LDL lowering.

The American Diabetes Association recommends that statins be considered for all people with type 2 diabetes over age 40 and for younger patients with risk factors. For patients with type 1 diabetes, use of statins should be considered even for children as young as age 10. In a recent meta-analysis conducted by the Cholesterol Treatment Trialists’ Collaboration, statins were shown to be effective in a wide range of patients with diabetes, irrespective of their absolute risk or whether they had type 1 or type 2 diabetes. All patients with diabetes should now be considered for statin therapy unless their risk is quite low, such as in younger children, or unless statin therapy is contraindicated, such as during pregnancy. The American Heart Association has also issued guidelines for the use of statins by children age 10 and older who meet certain high-risk criteria.

In late 2007, Crestor® was approved for slowing the progression of atherosclerosis, a novel indication among statin drugs. Slowing or reversing the progression of atherosclerosis is a surrogate marker for cardiovascular risk reduction. Thus far, only the highest daily doses of Lipitor® and Crestor have been shown to halt or possibly reverse atherosclerosis. As a result, higher doses of these drugs may be more commonly prescribed for this use.

### Treatment of low HDL cholesterol

Clinical trials of the combination drug torcetrapib/atorvastatin were halted in December 2006 when increased mortality compared with that for atorvastatin monotherapy was noted in the active treatment group of a Phase III trial. This unexpected finding, which some attributed to “off-target” effects of torcetrapib, was a major setback to the promising class of drugs known as cholesteryl ester transfer protein (CETP) inhibitors. Although the reasons for the increased mortality are not completely clear, two other CETP inhibitors, anacetrapib and dalcetrapib, are entering Phase III trials this year because of promising results from Phase II studies. However, neither of these drugs is likely to make it to market before 2011.

Several new combination products designed to either raise HDL cholesterol or lower LDL and raise HDL cholesterol at the same time are likely to be approved in the next 3 years. These new combination drugs include simvastatin/laropiprant/niacin extended release, laropiprant/niacin extended release, and rosuvastatin/ABT-335. Laropiprant is a prostaglandin D receptor antagonist that has been shown to reduce the flushing caused by niacin. Whether laropiprant will reduce niacin-induced flushing significantly more than aspirin or will significantly reduce long-term therapy discontinuations compared with niacin extended release alone remains to be determined. The success of these and other new combination products designed to raise HDL cholesterol and lower LDL cholesterol will hinge on the strength of emerging clinical evidence demonstrating cardiovascular benefits of raising HDL cholesterol with drug therapy.
The National Heart, Lung and Blood Institute is currently conducting a long-term outcome study to determine whether raising HDL cholesterol with drug therapy confers cardiovascular benefits. The AIM-HIGH study is a multicenter, randomized trial 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. The results of this study, which should be published in 2010 or 2011, will be critical to evaluating the validity of the hypothesis that raising HDL levels with niacin provides an advantage over lowering LDL levels with a statin alone.

Impact of new generics
First-time generics for both Zocor® (simvastatin) and Pravachol® (pravastatin) were introduced in 2006. By the end of 2007, the three generic statins—lovastatin, pravastatin, and simvastatin—accounted for slightly more than one-third of the prescription market in the statin class. These new generics will continue to moderate unit-cost growth as the product mix shifts toward lower-cost options over the next few years. However, higher dosage strengths of higher-potency brands and combination products that can lower LDL levels by more than 50% are still needed for many patients. For high-risk patients, more aggressive LDL goals (as low as 70 mg/dL) are recommended. Often, a drug that can lower LDL cholesterol by more than 50% will be needed to reach these goals.

ANTIHYPERTENSIVE DRUGS

Treatment rates
Antihypertensive agents as a class represent the largest single contributor to utilization in the cardiovascular category, and use of these drugs will continue to grow as a larger percentage of people with hypertension are diagnosed and treated. Hypertension is a very common disorder. From 2001 to 2004, among adults age 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. Nearly three-fourths of adults with cardiovascular comorbidities such as coronary artery disease, stroke, and diabetes have hypertension. Despite treatment rates in these patients of 75% or more, hypertension is controlled to target goals in only one-third to one-half of patients; thus, in many cases, hypertension further increases these patients’ already high cardiovascular risk.

Treatment options
Recent clinical studies suggest that patients who have coronary heart disease but not hypertension experience fewer cardiovascular events when taking certain antihypertensive drugs, such as ARBs and ACE inhibitors. Utilization of ARBs is likely to continue to increase rapidly because these drugs are known to be very well tolerated and are being employed more widely in patients who have had a heart attack or who have kidney disease or heart failure. Atacand is also being studied for its utility in preventing diabetic eye disease. FDA approval of this indication would create a completely new market for this product.

New drugs: Renin inhibitors
The first of a new generation of antihypertensive agents, Tekturna® (aliskiren), came to market in March 2007. Unlike the current agents that target angiotensin (ACE inhibitors and ARBs), this new drug acts on renin, an enzyme found at an earlier stage in the pathway leading to production of angiotensin II. Combination therapy using aliskiren and an ACE inhibitor or an ARB is being investigated. Aliskiren in combination with an ARB appears to produce greater reductions in blood pressure than either drug alone. Large outcome studies are underway to explore the potential benefits of aliskiren after heart attack and for primary and secondary prevention of cardiovascular disease. If the results of these studies are positive, aliskiren could more quickly displace ACE inhibitors and ARBs as a first-line option.

First-time generics
In March 2007, first-time generics were introduced for Norvasc® (amlodipine besylate), the most widely used dihydropyridine calcium channel blocker for the treatment of hypertension. Also in 2007, first-time generics for the popular products Toprol-XL® (metoprolol extended release) and Coreg® (carvedilol) became available. These new generics offer a significant opportunity to reduce unit costs in the antihypertensive category. However, availability of new brand-name combination...
products that combine amlodipine with an ARB (such as Azor™ and Exforge®) could reduce the potential savings from the new generics. Generic availability of ARBs is likely to begin with Cozaar® (losartan) in late 2010. Generics for some other drugs in the ARB class will follow in 2011 and 2012.

- **ANTICOAGULANT AND ANTIPLATELET DRUGS**

  **Treatment rates**
  The use of antiplatelet medications 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 will add to growth in this category over the next few years.

  **Marketplace dynamics**
  The excitement over a sustained early introduction of generics for Plavix® (clopidogrel) has now passed. The Plavix patent has been upheld, and generics for this drug may not reenter the marketplace until 2011. The focus has now shifted to new antiplatelet drugs that will serve as replacements for and possibly even improvements upon Plavix.

  Recent analyses make it clear that in patients with drug-eluting stents, Plavix and aspirin should be continued for at least 12 months after stent placement.34,35 In addition, recent results from a retrospective study suggest that a “rebound platelet effect” may occur when Plavix is discontinued. This evidence suggests that during the first 90 days after Plavix is discontinued, the risk of cardiovascular events increases.36 Therefore, it is reasonable to expect that there will be hesitancy to discontinue Plavix treatment until the issue is resolved or a better way to discontinue Plavix is found. Thus, more patients may remain on this drug longer after stent placement or after admission for acute coronary syndrome, contributing to increased utilization.

  **New drugs**
  Prasugrel and ticagrelor, new pipeline antiplatelet drugs which, like Plavix, act at the adenosine diphosphate receptor, are being studied in a variety of settings. Both of these drugs are likely to be introduced before the patent for Plavix expires in 2011. A major study comparing prasugrel and clopidogrel has recently been published.37 In patients with acute coronary syndrome 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 was reported with prasugrel, including fatal bleeding. Because the risk of bleeding is low in patients with acute coronary syndrome with scheduled percutaneous coronary intervention, prasugrel may quickly replace clopidogrel, at least for these patients.

  A new antiplatelet agent, SCH 53034, with a unique mechanism of action—thrombin receptor inhibition—could also come to market. Current evidence indicates that this drug will be used in addition to current standard therapy, such as clopidogrel and aspirin, in patients with acute coronary syndrome. Since this drug is likely to be an add-on therapy, it could increase cost and utilization in the antiplatelet category starting in 2010.

  Several novel oral anticoagulants are in the near-term pipeline. These include rivaroxaban and apixaban, both oral Factor Xa inhibitors, and dabigatran, a reversible direct thrombin inhibitor. The drug that is closest to market, rivaroxaban, has shown unprecedented efficacy with no compromise in safety in several Phase III orthopedic surgery studies comparing it with the current standard, Lovenox® (an injectable). Also, none of the new oral anticoagulants will require the type of intensive monitoring that warfarin (Coumadin®) does, giving them a very significant advantage. These drugs could be used for such purposes as preventing or treating deep vein thrombosis and pulmonary embolism after orthopedic surgery, and preventing stroke in patients with atrial fibrillation. When approved, these agents are likely to become the standard of care, significantly increasing both utilization and unit cost in the oral anticoagulant drug category, which is currently dominated by warfarin.
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>2008</td>
<td>niacin + laropiprant</td>
<td>High cholesterol, low HDL</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>tolvaptan</td>
<td>Hyponatremia, congestive heart failure</td>
<td>$</td>
</tr>
<tr>
<td>2009</td>
<td>prasugrel</td>
<td>Prevention of stroke and myocardial infarction (MI) in patients after percutaneous coronary intervention</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>niacin extended release + simvastatin + laropiprant</td>
<td>High cholesterol, low HDL</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>dabigatran</td>
<td>Prevention and treatment of deep-vein thrombosis, pulmonary embolism</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td>choline fenofibrate</td>
<td>Low HDL, high triglycerides</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>rivaroxaban</td>
<td>Prevention and treatment of deep-vein thrombosis, pulmonary embolism</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td>dronedarone</td>
<td>Ventricular arrhythmias</td>
<td>$</td>
</tr>
<tr>
<td>2010</td>
<td>bucindolol</td>
<td>Congestive heart failure</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>apixaban</td>
<td>Prevention and treatment of deep-vein thrombosis, pulmonary embolism</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>LY517717</td>
<td>Prevention and treatment of deep-vein thrombosis, pulmonary embolism</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>SCH 530348</td>
<td>Secondary prevention of stroke, MI</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td>ticagrelor</td>
<td>Secondary prevention of stroke, MI</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>choline fenofibrate + rosvastatin</td>
<td>High cholesterol, low HDL, high triglycerides</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td>darusentan</td>
<td>High blood pressure</td>
<td>$</td>
</tr>
</tbody>
</table>

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

CNS agents

Contribution to plan spending (2007): 22.7%  
Projected contribution to trend (2008 to 2010): 27%

Projected trend

Table 6. Drug trend projection for CNS agents*

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utilization increase</td>
<td>4% to 5%</td>
<td>4% to 5%</td>
<td>4% to 5%</td>
</tr>
<tr>
<td>Price and mix increase</td>
<td>5% to 6%</td>
<td>4% to 5%</td>
<td>5% to 6%</td>
</tr>
<tr>
<td>Annual total</td>
<td>9% to 11%</td>
<td>8% to 10%</td>
<td>9% to 11%</td>
</tr>
</tbody>
</table>

* Projected change in drug spending on an AWP 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 treatment rates for sedative-hypnotics and antiseizure medications
- Many new drugs for the treatment of epilepsy, schizophrenia, attention deficit hyperactivity disorder, depression, and insomnia
- Reformulations of narcotic pain relievers aimed at less abuse potential
- Elimination of generics for the popular long-acting narcotic OxyContin® (oxycodone controlled release)
- First-time generics for Risperdal®, a commonly used antipsychotic agent, and up to five antiseizure drugs—Tegretol®-XR, Depakote®, Keppra, Lamictal, and Topamax®

Trend drivers: Sleep agents, antiseizure medications, narcotic pain relievers, atypical antipsychotics
Trend moderators: Antianxiety agents, nonsteroidal anti-inflammatory drugs (NSAIDs)

SEDATIVE-HYPNOTICS

Treatment of insomnia

No new insomnia treatments were approved by the FDA in 2007, but utilization of these drugs continues to increase, partly because of aggressive marketing of Lunesta® (eszopiclone), Ambien CR® (zolpidem controlled release), and Rozerem™ (ramelteon). Utilization increases may also be due to increased treatment rates for insomnia, which has been estimated to affect one-third of the U.S. population. Utilization of these agents is likely to grow 7% per year over the next 3 years.

New drugs for insomnia

Silenor™ (doxepin extended release), a reformulated antidepressant, may be introduced in 2008 as a treatment for insomnia. Silenor is different from other hypnotics because it does not work on the benzodiazepine receptor, so it is unlikely to be designated a controlled substance. Indiplon, an agent that is similar to zolpidem, was expected to reach the market in 2008, but because the FDA has requested additional data, this drug may not be approved until 2009 or 2010. Finally, eplivanserin, a serotonin receptor antagonist that has a different mechanism of action from currently available sedative-hypnotics, may be approved by 2010.

First-time generics

The availability of first-time generics for Ambien® (zolpidem) has moderated unit-cost growth for sedative-hypnotics. Generic versions were introduced in April 2007, and by the end of 2007, generic zolpidem accounted for 45% of all sedative-hypnotic prescriptions. However, share shifts to single-source brands represent a continued threat to the use of generic zolpidem products.

SEIZURE MEDICATIONS

Broader indications

Utilization of anticonvulsant drugs continues to grow briskly, partly because of the increased use of these drugs for nonseizure indications and the increased use of combination therapy for refractory seizure disorders. Nonseizure conditions for which anticonvulsants are being studied and used include neuropathic pain, migraine headache prevention, and certain psychiatric conditions, such as bipolar disorder. In June 2007, Lyrica® (pregabalin) became the first drug to be approved for fibromyalgia, a very common disorder characterized by chronic widespread pain. The new indication is expected to increase use of this drug.
**New anticonvulsants**

Several new anticonvulsants are expected to be introduced over the next 3 years and will contribute to continued utilization growth in this category. Rufinamide (expected in 2008) is being studied as a treatment for partial-onset seizures and for Lennox-Gestault syndrome, a rare but severe seizure disorder. Lacosamide (also expected in 2008) has a novel mechanism of action and a favorable drug interaction profile, and it may be approved for seizure disorders as well as diabetic neuropathy. Retigabine, a gamma-aminobutyric acid and potassium channel agonist, and carisbamate, a follow-on product to Topamax, are both expected to come to market in 2009.

New extended-release formulations of levetiracetam, lamotrigine, and gabapentin are expected in 2008. These long-acting versions may offer increased patient convenience through once-daily dosing but may reduce potential savings from generic versions that are or will become available in the next 2 years.

**First-time generics**

First-time generics may enter the market in late 2008 for Tegretol-XR (carbamazepine extended release), Depakote (divalproex), and Keppra (levetiracetam). Additional first-time generics are expected in 2009 when patents expire on Topamax (topiramate) and Lamictal (lamotrigine). These five antiseizure medications accounted for approximately $5.5 billion in U.S. sales in 2007 and represent a significant savings opportunity for plans. However, new follow-on products and anti–generic-substitution initiatives in the antiseizure category represent real threats to these savings.

**Antidepressants**

Utilization of antidepressants is likely to grow slowly over the next 3 years. In spite of the lack of clear evidence of their superiority over other antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs) are likely to generate most of the growth in the category. The utilization of selective serotonin reuptake inhibitors (SSRIs) is likely to remain flat. New indications for the SNRI antidepressants—including seasonal affective disorder, neuropathic pain, and fibromyalgia—will contribute to expanded utilization in this class.

**New antidepressants**

In 2009, the market could see three new medications that work differently from the antidepressants available today. Saredutant is a neurokinin-2 receptor blocker that has antidepressant and antianxiety properties. Agomelatine is a melatonin agonist/serotonin antagonist that may also have beneficial effects on sleep patterns. Amibegron stimulates the beta 3-adrenoceptor in the brain and has antidepressant plus antianxiety properties. Amibegron may also affect gastrointestinal motility, which could be beneficial in obesity and diabetes. Although these agents have novel mechanisms of action, they have not yet been shown to be more effective than currently available antidepressants. However, more brand-name drugs in the class portend rising unit costs over the next 3 years.

Fibromyalgia, which affects approximately 1% to 5% of the U.S. population, has also been a focus of drug development. Milnacipran (expected late 2008) is a new SNRI that may relieve pain and improve physical function for patients with fibromyalgia. Cymbalta (duloxetine), another SNRI, is also being studied for use in fibromyalgia and may gain approval for this indication before milnacipran becomes available.

Pristiq™ (desvenlafaxine), a follow-on product containing the active metabolite of Effexor® (venlafaxine), was approved in February 2008 for the treatment of depression and may be approved in 2009 for the treatment of vasomotor symptoms of menopause.

**First-time generics**

The average unit cost of antidepressants has been declining due to the widespread availability of generic antidepressants. Generic versions of Paxil CR® (paroxetine controlled release) are expected in the second half of 2008.
**ANTIPSYCHOTICS**

Atypical antipsychotic agents are expected to show only low single-digit utilization growth over the next 3 years. In addition to being used to treat schizophrenia, many of these medications are also approved for short- and long-term treatment of mania associated with bipolar disorder. In November 2007, Abilify® (aripiprazole) became the first atypical antipsychotic to be approved as adjunctive treatment for major depressive disorder in adults. Unapproved uses for these drugs include obsessive-compulsive disorder, post-traumatic stress disorder, personality disorders, and dementia.

**New antipsychotics**

Several new antipsychotic agents may come to market in the next few years. Iloperidone (expected in 2008) 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. Asenapine (expected in early 2009) may be similar to Clozaril® in efficacy, but may have potentially fewer side effects. Bifeprunox, which initially received a nonapprovable letter in 2007, is expected to be available by 2010. Bifeprunox is similar to other atypical antipsychotics but may cause less weight gain and fewer metabolic side effects than currently available products.

**First-time generics**

Unit-cost growth for antipsychotics will be moderated by the availability of generic versions of Risperdal (risperidone), which are likely to be introduced in 2008. Risperdal, a popular atypical antipsychotic, accounted for approximately $2 billion in drug sales in 2007.® Invega®, a follow-on compound for Risperdal, has not made significant inroads into Risperdal sales, so much of the Risperdal market has been preserved for generic substitution. No other new generics are expected in this category during the next 3 years.

**ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)**

Treatment rates for ADHD continue to grow rapidly. Approximately 7.8% of U.S. school-aged children (age 4 to 17) have received an ADHD diagnosis, and about 4.3% of children currently take medication for this condition. Approximately 4.4% of young adults (age 18 to 44) have ADHD, but only 1.2% of adults in this age group are currently taking medication for this disorder.

Two new ADHD drugs could be introduced in 2008, and both are being studied in the adult population. Guanfacine, an antihypertensive drug that 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. SPD-465 is a longer-acting (up to 16 hours) formulation of Adderall XR® that may be useful for adults with long work days.

**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 remains the only available COX-2 inhibitor on the market, and no others are expected to be approved in the next 3 years. Etoricoxib and lumiracoxib, which were both reviewed by the FDA in 2007, were denied approval because of safety concerns.

Drug development in the NSAID category is focusing on drug combinations that may help protect against gastrointestinal toxicity. An ibuprofen/famotidine combination may be approved in 2009 and a naproxen/esomeprazole combination in 2010. Naproxcinod is a novel form of naproxen that releases nitric oxide in the intestine. It was designed to protect against NSAID-induced ulcers. Tapentadol, a nonnarcotic analgesic similar to tramadol, is expected in 2009. Utilization growth for the nonnarcotic analgesics will probably continue at a moderate pace over the next 3 years.
NARCOTIC PAIN RELIEVERS

Utilization of narcotic pain relievers is likely to increase approximately 10% per year over the next 3 years. Products in the pipeline include reformulations of currently available narcotics, some of which are designed to have less potential for abuse. Remoxy®, a new extended-release version of oxycodone, contains a gel cap that appears to be resistant to dissolution with alcohol and cannot be crushed. Embeda™ (morphine sulfate/naltrexone) is an abuse-resistant formulation of morphine; crushing of Embeda releases naltrexone (a morphine antagonist) from the bead cores, blocking the effects of morphine. Oxytrex™, anticipated in 2010, is a new formulation of oxycodone that contains 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. However, none of the products in the pipeline is expected to provide a significant advantage over currently available narcotic pain relievers.

First-time generics
Generic versions of OxyContin (oxycodone) remained available in 2007, but production was halted because of patent litigation and settlements between the brand and generic manufacturers. After the existing supply is exhausted in early 2008, only the brand-name product will be available; generic versions of OxyContin are not expected to return to the market until after 2010.

ALZHEIMER’S DEMENTIA

Utilization of drugs for Alzheimer’s disease continues to grow at a rate of about 8% per year, reflecting increased use of Aricept® and Namenda®. The pipeline features several drugs that may have disease-modifying properties and may provide an advantage over currently available agents, which deliver only modest symptomatic relief but have not been shown to alter disease progression. Flurizan® (expected in 2010), the R-isomer of the NSAID flurbiprofen, reduces levels of insoluble beta-amyloid in the brain, and early studies indicate a slowing of disease progression among patients with mild Alzheimer’s dementia. Tramiprosate (also expected in 2010) binds to glycosaminoglycan (GAG) proteins and prevents them from binding to beta-amyloid. GAGs have been shown to promote the formation of beta-amyloid plaques in the brain. Other disease-modifying drugs are also in development, including a monoclonal antibody known as bapineuzumab, which is targeted against beta-amyloid, but none of these agents is likely to reach the market in the next 3 years.

First-time generics
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 billion in sales in 2007 and is the most popular of the cholinesterase inhibitors. First-time generics for Namenda (memantine), which accounted for approximately $500 million in sales in 2007, may be available in 2010.

PARKINSON’S DISEASE

Several drugs with new mechanisms may become available for the treatment of Parkinson’s disease in the next 3 years. Perampanel is an alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist that may be available in 2010. Safinamide, another pipeline drug, appears to have multiple mechanisms of action, including selective inhibition of monoamine oxidase-B reuptake and dopamine reuptake. Safinamide, which is being studied as an adjunct to dopamine agonist therapy, may be available in 2010. Finally, Requip XL™ (ropinirole extended release), a once-daily formulation of Requip®, may be approved for Parkinson’s disease and restless legs syndrome in 2008. Requip, which accounted for $414 million in drug expenditures in 2007, is scheduled to lose patent protection in 2008.

MULTIPLE SCLEROSIS (MS)

Several new MS drugs may come to market over the next few years. Sustained-release fampridine (4-aminopyridine) blocks potassium channels in nerves and may increase walking distance for patients with more advanced MS. Fampridine
may be introduced in late 2009 or early 2010. Fingolimod (expected in 2010) is a once-daily oral immunosuppressant that lowers the levels of activated T-cells in the bloodstream and in the CNS. An oral formulation of cladribine indicated for MS is expected in 2010. Cladribine, a chemotherapeutic agent, has been used off-label as a treatment for MS but currently 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.

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>2008</td>
<td>asenapine</td>
<td>Schizophrenia, bipolar disorder</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>guanfacine extended release</td>
<td>ADHD</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>iloperidone</td>
<td>Schizophrenia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>lacosamide</td>
<td>Neuropathic pain, seizure disorders</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>lamotrigine extended release</td>
<td>Seizure disorders, bipolar disorder</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>levetiracetam extended release</td>
<td>Seizure disorders</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>gabapentin extended release</td>
<td>Seizure disorders, neuropathic pain</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>milnacpran</td>
<td>Fibromyalgia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>morphine extended release + naltrexone</td>
<td>Pain</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>oxycodone extended release (abuse-resistant formulation)</td>
<td>Chronic pain</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ropinirole extended release</td>
<td>Restless legs syndrome, Parkinson's disease</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>rufinamide</td>
<td>Seizure disorders</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>SPD-465</td>
<td>ADHD in adults</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>tetrabenazine</td>
<td>Huntington's disease</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>doxepin extended release</td>
<td>Insomnia</td>
<td>$</td>
</tr>
<tr>
<td>2009</td>
<td>agomelatine</td>
<td>Depression</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>amibegron</td>
<td>Depression, anxiety</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>desvenlafaxine</td>
<td>Vasomotor symptoms of menopause</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>fampridine sustained release</td>
<td>Multiple sclerosis</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>tapentadol</td>
<td>Moderate-to-severe pain</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ibuprofen + famotidine</td>
<td>Mild-to-moderate pain</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>indiplon</td>
<td>Insomnia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>retigabine</td>
<td>Seizure disorders</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>saredutant</td>
<td>Depression</td>
<td>$</td>
</tr>
<tr>
<td>2010</td>
<td>bifeprunox</td>
<td>Schizophrenia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>cladribine (oral)</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>tramiprosate</td>
<td>Alzheimer's disease</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>naproxcinod</td>
<td>Osteoarthritis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>naproxen + esomeprazole</td>
<td>Pain</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>oxycodone + naltrexone</td>
<td>Chronic pain</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>safinamide</td>
<td>Parkinson's disease</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>eplivanserin</td>
<td>Insomnia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>R-flurbiprofen</td>
<td>Alzheimer's disease</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>perampanel</td>
<td>Parkinson's disease</td>
<td>$</td>
</tr>
</tbody>
</table>

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

Contribution to plan spending (2007): 8.4%
Projected contribution to trend (2008 to 2010): 10%

Projected trend

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

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utilization increase</td>
<td>5% to 6%</td>
<td>4% to 5%</td>
<td>3% to 4%</td>
</tr>
<tr>
<td>Price and mix increase</td>
<td>5% to 6%</td>
<td>6% to 7%</td>
<td>5% to 6%</td>
</tr>
<tr>
<td>Annual total</td>
<td>10% to 12%</td>
<td>10% to 12%</td>
<td>8% to 10%</td>
</tr>
</tbody>
</table>

*T Projected change in drug spending on an AWP 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 increased diagnosis and treatment of diabetes
- Increased use of multiple-drug therapy to help control blood glucose levels and prevent complications of diabetes
- Introduction of several new products, both oral agents and injectables, for the treatment of diabetes and its complications
- Very limited first-time generic introductions

Trend drivers: Oral hypoglycemic agents, insulin products

DIABETES

Obesity and diabetes
Diabetes has become increasingly prevalent over the past 20 years. The American Diabetes Association estimates that diabetes has been diagnosed in approximately 17.5 million people in the United States, an increase of almost 45% from the 2002 estimate of 12.1 million people. If one compares the 2007 estimate with the 2002 estimate, the number of people with diagnosed diabetes is growing by a staggering 1 million people per year.

The increase in diabetes prevalence is generally attributed to the epidemic of obesity in the United States. Nearly nine out of ten people with newly diagnosed type 2 diabetes are overweight. The potential future increase in the number of patients with diabetes, as reflected in obesity statistics, is overwhelming. During the period 2003–2004, about 67% of adults between the ages of 20 and 74 were overweight and 34% were considered obese. When similar criteria are used, about 30% of children and adolescents between the ages of 6 and 19 are overweight, with about 15% meeting the criteria for obesity.

Dietary modifications and regular exercise can delay or prevent the development of diabetes, but these lifestyle changes are often too difficult for people 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 medications over the next several years.

In spite of the availability of numerous medications to help treat diabetes, only 7% 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 medications—including oral and injectable hypoglycemic agents, insulin products, and drugs that help manage the complications of diabetes.

**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. Two- and three-drug combinations are frequently required to help patients achieve adequate blood glucose control. A long-term clinical trial has recently indicated that tight control of blood glucose levels may reduce the macrovascular, as well as microvascular, complications of diabetes. However, in spite of the anticipated benefits of lowering the A1C levels of diabetic patients to those of nondiabetics, an ongoing study in type 2 diabetics was prematurely halted because of an increased risk of death among patients who were aggressively lowering their A1C levels to below 6%. The researchers have extensively analyzed the available data but have not been able to identify any specific cause for the higher death rate among the intensively treated group. As a result, physicians may be reluctant to lower their patients’ A1C levels below 6.5% until more clinical data are available. Today, the vast majority of patients with diabetes do not achieve A1C levels below 7%, so progress is still needed in terms of improving their glycemic control.

**Inhaled insulin**

The first inhaled insulin product, Exubera®, received FDA approval in January 2006 and became commercially available during the third quarter of that year. However, one year after the launch of Exubera, Pfizer unexpectedly elected to withdraw it from the market because of low physician and patient acceptance. In addition, novo nordisk and Lilly have both announced that they are terminating clinical development of their inhaled insulin products. Therefore, an inhaled insulin product is unlikely to be introduced during the next several years.

**New injectables**

Two novel injectable hypoglycemic agents for diabetes were introduced in 2005—Byetta® (exenatide) and Symlin® (pramlintide). Byetta, a glucagon-like peptide-1 agonist, has multiple effects on blood glucose control. It stimulates the secretion of insulin in the presence of elevated blood glucose, slows gastric emptying to delay entry of ingested sugar into the bloodstream, and inhibits secretion of glucagon. Over time, the use of Byetta leads to weight loss—an unusual benefit among drugs used to treat diabetes.

Another new injectable agent, liraglutide, is currently in Phase III clinical development and may be introduced in early 2009. Liraglutide acts similarly to Byetta but is administered only once daily and seems to produce similar A1C reduction and weight loss. A once-weekly dosage form of exenatide called Byetta® LAR is also in clinical development and could be approved by the FDA in late 2009 or early 2010. A once-weekly injectable for the treatment of diabetes would be a revolutionary advance and would probably be widely utilized.

**Dipeptidyl peptidase IV (DPP-IV) inhibitors**

DPP-IV inhibitors are likely to be used in multiple-drug combination treatments 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 various stages of clinical development, including alogliptin, saxagliptin, vildagliptin, and vildagliptin/metformin. These drugs may be approved over the next 3 years, but recent FDA demands for more data on vildagliptin could cause Novartis to abandon further development of this compound.

**Thiazolidinediones**

The two current glitazone products—Actos® (pioglitazone) and Avandia® (rosiglitazone)—are likely to see slower growth than in the past because of recent safety concerns and a black box warning about the potential for these drugs to increase the risk of congestive heart failure. In addition, sales of Avandia have declined substantially since June 2007 as a result of clinical data and a black box warning about a possible increased risk of heart attacks and heart-related deaths in patients using the drug.
Additional glitazone products are unlikely to be approved in the near future, given the many questions and safety concerns surrounding Avandia and Actos. In addition, most of the glitazone drugs in clinical development have been halted or stopped because of adverse events.57

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>2008</td>
<td>alogliptin</td>
<td>Type 2 diabetes</td>
<td>$</td>
</tr>
<tr>
<td>2009</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>$</td>
</tr>
<tr>
<td></td>
<td>liraglutide</td>
<td>Type 2 diabetes</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>exenatide long-acting formulation (Byetta® LAR)</td>
<td>Type 2 diabetes</td>
<td>$</td>
</tr>
<tr>
<td>2010</td>
<td>vildagliptin</td>
<td>Type 2 diabetes</td>
<td>$</td>
</tr>
</tbody>
</table>

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

Gastroenterology drugs

Contribution to plan spending (2007): 9.2%
Projected contribution to trend (2008 to 2010): 4%

Projected trend

Table 10. Drug trend projection for gastroenterology agents*

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utilization increase</td>
<td>1% to 2%</td>
<td>1% to 2%</td>
<td>0% to 1%</td>
</tr>
<tr>
<td>Price and mix increase</td>
<td>3% to 4%</td>
<td>2% to 3%</td>
<td>3% to 4%</td>
</tr>
<tr>
<td>Annual total</td>
<td>4% to 6%</td>
<td>3% to 5%</td>
<td>3% to 5%</td>
</tr>
</tbody>
</table>

* Projected change in drug spending on an AWP PMPY basis

TREND PREDICTIONS

Key developments that are likely to shape drug trend in the gastroenterology category over the next 3 years:
- First-time generics for Protonix®, Prevacid, and AcipHex®
- Partial OTC conversion for Prevacid (lansoprazole)
- A new specialty drug called certolizumab pegol, a tumor necrosis factor (TNF) inhibitor, for the treatment of Crohn’s disease

Trend driver: Proton pump inhibitors
Trend moderator: H₂ antagonists
■ **ULCER AND HEARTBURN**

A generic version of a leading proton pump inhibitor, Protonix (pantoprazole), unexpectedly became available at the beginning of 2008. This new generic drug will help moderate treatment costs for acid peptic disorders. The long-term availability of generic pantoprazole will be determined in court, but a decision is not expected until the end of 2008. First-time generics for Prilosec® (omeprazole) 40-mg delayed-release tablets may become available in 2008 or 2009. AcipHex (rabeprazole) and Prevacid (lansoprazole) are expected to lose their patent protection and become available in generic form toward the end of 2009.

A follow-on compound for Prevacid, TAK-390MR, is currently in clinical development for the treatment of gastroesophageal reflux disease and peptic ulcer. TAK-390MR is a single enantiomer version of Prevacid that uses a new release technology.

■ **CHRONIC CONSTIPATION**

In January 2006, Amitiza® (lubiprostone) was approved for the treatment of chronic constipation, a disorder that affects millions of Americans. After Zelnorm® was withdrawn from the market in March 2007, Amitiza became the only FDA-approved drug for this condition. This drug is likely to generate moderate utilization growth in the gastroenterology category over the next 3 years. Renzapride, which is under clinical development for the treatment of constipation-related irritable bowel syndrome, may receive approval from the FDA in late 2009 or early 2010.

■ **INFLAMMATORY BOWEL DISEASE**

New indications for biologic agents to be used in the treatment of inflammatory bowel disease, which affects almost 1 million people in the United States, will contribute to increased utilization over the next 3 years. In February 2007, Humira® was approved for the treatment of Crohn’s disease in adults, and in January 2008, Tysabri® received an additional second-line indication for the treatment of moderate-to-severe Crohn’s disease.

A new specialty medication, certolizumab pegol (Cimzia®), has faced some regulatory issues with its NDA submission but may still receive FDA approval in 2008 for the treatment of Crohn’s disease. Cimzia is a once-monthly, subcutaneously administered, pegylated anti-TNF antibody with actions similar to those of Humira. Cimzia is also under clinical evaluation for the treatment of rheumatoid arthritis. The costs for this drug will appear in the gastroenterology chapter because Crohn’s disease is likely to be its first approved indication.

Table 11. Some ambulatory-use gastroenterology 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>2008</td>
<td>certolizumab pegol methylaltrexone</td>
<td>Crohn’s disease, Opioid-induced constipation</td>
<td>$</td>
</tr>
<tr>
<td>2009</td>
<td>TAK-390MR renzapride tolevamer</td>
<td>GERD, stomach ulcers, Constipation-predominant irritable bowel syndrome Clostridium difficile–associated diarrhea</td>
<td>$</td>
</tr>
<tr>
<td>2010</td>
<td>teduglutide</td>
<td>Short bowel syndrome</td>
<td>$</td>
</tr>
</tbody>
</table>

$% = potential to cause a % increase in this category’s trend.
$% = potential impact % increase in this category’s trend.
Bold text indicates potential specialty drug.
Musculoskeletal and rheumatological agents

Contribution to plan spending (2007): 5.3%
Projected contribution to trend (2008 to 2010): 4%

Projected trend

Table 12. Drug trend projection for musculoskeletal and rheumatological agents*

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utilization increase</td>
<td>1% to 2%</td>
<td>0% to 1%</td>
<td>1% to 2%</td>
</tr>
<tr>
<td>Price and mix increase</td>
<td>8% to 9%</td>
<td>4% to 6%</td>
<td>6% to 7%</td>
</tr>
<tr>
<td>Annual total</td>
<td>9% to 11%</td>
<td>4% to 7%</td>
<td>7% to 9%</td>
</tr>
</tbody>
</table>

* Projected change in drug spending on an AWP PMPY basis

TREND PREDICTIONS

Key developments that are likely to shape drug trend for musculoskeletal and rheumatological drugs over the next 3 years:
- Higher doses and earlier use of both existing and pipeline biologics, such as Enbrel, Humira, golimumab, and tocilizumab, for the treatment of rheumatoid arthritis
- Increased use of biologics for an expanding range of indications, including chronic plaque psoriasis, Crohn's disease, and other immunologic disorders in which TNF is thought to be a mediator of disease
- Introduction of several new specialty and nonspecialty treatments for osteoporosis
- First-time generics for Fosamax (alendronate), the market-leading osteoporosis treatment

Trend driver: TNF inhibitors
Trend moderator: Bisphosphonates

OSTEOPOROSIS

Treatment trends
An estimated 44 million Americans have osteoporosis or are at risk for it. Plan spending for this treatment class is expected to grow by 4% to 5% per year over the next 3 years, driven mainly by price inflation for single-source brands.

Once-weekly bisphosphonates, such as Fosamax and Actonel®, account for more than 75% of bisphosphonate use and nearly one-half of the total utilization of osteoporosis drugs, with Fosamax currently the market leader. Evista® (raloxifene), Miocalcin® (calcitonin), Fortical® (calcitonin), and Forteo® (teriparatide) are also used to treat osteoporosis, but these drugs account for a smaller share of overall utilization. Forteo has recently been shown to increase bone mineral density to a greater extent than alendronate in patients with glucocorticoid-induced osteoporosis. To date, only a single case of osteogenic sarcoma has been possibly linked to use of this drug.

SERMs: Old and new
Evista (raloxifene) was the first selective estrogen receptor modulator (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. Results of the study supporting this indication, the Study of Tamoxifen and Raloxifene (STAR) trial, suggest that raloxifene is similar to tamoxifen in its ability to reduce the incidence of breast cancer.
In September 2005, a second SERM, lasofoxifene, received a nonapprovable letter from the FDA because of concerns about its association with endometrial thickening. The manufacturer resubmitted the NDA this year for an osteoporosis treatment indication, based on 3-year interim results of a large clinical trial. Lasofoxifene could win FDA approval in 2009.

Two newer SERMs, bazedoxifene and arzoxifene, are also in late-stage clinical development. Approval of bazedoxifene is expected this year, and a combination product of bazedoxifene and conjugated estrogens may be approved in 2009. The combination product, which may cause minimal endometrial thickening, is intended to help alleviate postmenopausal symptoms that might be worsened by bazedoxifene alone. The second new SERM, arzoxifene, is currently 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. It is not clear yet whether these newer compounds will outperform Evista in terms of fracture reduction or breast cancer prevention.

New specialty drugs for osteoporosis
A new specialty injectable drug for the treatment and prevention of osteoporosis, denosumab, may be introduced in 2010. Denosumab is a monoclonal antibody that 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 this drug may equal or exceed Fosamax as an agent for increasing bone mineral density.63 Additionally, data from a recently concluded study suggest that denosumab is effective in building bone mineral density in patients with breast cancer who are undergoing treatment with chemotherapeutic agents known to accelerate bone loss and increase fracture risk.64 Denosumab is self-administered by injection only twice a year, so it could be well accepted by patients and prescribers, especially if it proves to be well tolerated by patients. Whether the fracture risk reduction with denosumab will rival that with the bisphosphonates remains to be seen, but the available data are promising.

A once-yearly injectable formulation of zoledronic acid (Reclast®) was approved in 2007 for the treatment of osteoporosis. This drug has robust efficacy and safety data, and once-yearly administration will be a convenience for some patients.

First-time generics
Generic versions of Fosamax (alendronate) were introduced in early 2008. New generics are likely to have a significant impact on unit costs, since there appear to be few clinical reasons to select other oral bisphosphonates over alendronate. The link between bisphosphonates and osteonecrosis of the jaw has been noted primarily with intravenous bisphosphonates used in patients with cancer.65 There is no clear evidence that this safety issue is more common with one oral bisphosphonate than another.

RHEUMATOID ARTHRITIS

Treatment trends
Rheumatoid arthritis is a common condition affecting more than 2 million Americans.66 Many of these patients are candidates for treatment with a biologic agent, such as Enbrel, Humira, or Remicade®. These agents are revolutionary in that they offer the promise of controlling rheumatic diseases to an extent not previously possible.

Biologic agents are being used much earlier and more frequently in rheumatoid arthritis treatment, as results from clinical trials continue to demonstrate the excellent efficacy and safety profiles of these drugs.67 Early use of combination therapy (such as methotrexate with either Enbrel or Humira) improves symptoms and slows disease progression more than either drug alone and is gaining support in the medical community.

New indications for biologics
Enbrel is in clinical trials for several additional indications, including the treatment of idiopathic pulmonary fibrosis, a rare but severe disease for which there are few treatment options. Humira received FDA approval for the treatment of Crohn’s disease in March 2007 and for chronic plaque psoriasis in early 2008. Both Humira and Enbrel are in clinical development for the treatment of asthma. FDA approval of these new indications will fuel utilization of these self-administered biologics.
**New specialty drugs**

Several new drugs targeting T-cell and B-cell activity are in the near-term pipeline for rheumatoid arthritis and other autoimmune conditions:

- Two new anti-cathepsin D 20 monoclonal antibodies, ocrelizumab and ofatumumab, are in clinical development and could be available by 2010. These intravenously administered drugs work by interfering with B-cell activity and have been manufactured to closely resemble naturally occurring human antibodies, thus enhancing their tolerability and effectiveness.

- Certolizumab pegol (*Cimzia*) may be approved for the treatment of rheumatoid arthritis by 2009. The results of two large clinical trials suggest that the combination of *Cimzia* and methotrexate is very effective in delaying the progression of rheumatoid arthritis and improving physical function.68

- Golimumab, a fully humanized monoclonal anti-TNF antibody, which could be available in both intravenous and subcutaneous formulations that a patient can self-administer, is in clinical development for rheumatoid arthritis and psoriatic arthritis. This drug is likely to be introduced by early 2009.

**Novel interleukin antagonists**

Inhibitors of various interleukins, including interleukin 1, interleukin 6, and interleukin 12, are an area of new drug development for the treatment of immune-mediated diseases, such as rheumatoid arthritis, plaque psoriasis, and cryopyrin-associated periodic syndromes. Tocilizumab, an anti-interleukin-6-receptor monoclonal antibody in clinical development for rheumatoid arthritis, could be introduced in 2009. This intravenously administered drug has shown efficacy in Phase III trials and is already available in Japan. Tocilizumab may also prove useful in treating Crohn’s disease and other immune-mediated disorders.

Table 13. 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>2008</td>
<td>febuxostat</td>
<td>Hyperuricemia in chronic gout</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>bazedoxifene</td>
<td>Osteoporosis</td>
<td>$</td>
</tr>
<tr>
<td>2009</td>
<td>lasofoxifene</td>
<td>Osteoporosis, vaginal atrophy</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>golimumab</td>
<td>Rheumatoid arthritis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>bazedoxifene + conjugated estrogen</td>
<td>Osteoporosis, postmenopausal symptoms</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>abatacept (subcutaneous formulation)</td>
<td>Rheumatoid arthritis refractory to TNF inhibitors</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>tocilizumab</td>
<td>Rheumatoid arthritis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>certolizumab pegol</td>
<td>Rheumatoid arthritis</td>
<td>$</td>
</tr>
<tr>
<td>2010</td>
<td>denosumab</td>
<td>Osteoporosis, bone metastases</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>arzoxifene</td>
<td>Osteoporosis, breast cancer</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ospemifene</td>
<td>Vaginal atrophy</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>epratuzumab</td>
<td>Lupus erythematosus</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>abetimus</td>
<td>Lupus erythematosus</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>clodronate</td>
<td>Bone metastasis in breast cancer, hypercalcemia of malignancy</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ocrelizumab</td>
<td>Rheumatoid arthritis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ofatumumab</td>
<td>Rheumatoid arthritis</td>
<td>$</td>
</tr>
</tbody>
</table>

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

Contribution to plan spending (2007): 9.1%
Projected contribution to trend (2008 to 2010): 5%

Projected trend

Table 14. Drug trend projection for respiratory agents*

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Utilization increase</td>
<td>0% to 1%</td>
<td>0% to 1%</td>
</tr>
<tr>
<td></td>
<td>Price and mix increase</td>
<td>3% to 4%</td>
<td>3% to 4%</td>
</tr>
<tr>
<td></td>
<td>Annual total</td>
<td>3% to 5%</td>
<td>3% to 5%</td>
</tr>
</tbody>
</table>

*T Projected change in drug spending on an AWP PMPY basis

Trend predictions

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

- New 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 oral and inhaled treatments for pulmonary arterial hypertension and cystic fibrosis
- Conversion of Zyrtec, Zyrtec-D®, and possibly Clarinex to OTC status

Trend driver: Miscellaneous pulmonary agents
Trend moderator: Nonsedating antihistamines

Asthma and Chronic Obstructive Pulmonary Disease (COPD)

Treatment trends

Recent guidelines for the treatment of asthma confirm that inhaled corticosteroids are the preferred agents for long-term control of asthma in children and adults. Long-acting beta-agonists are not recommended for monotherapy, but are recommended for use in combination with inhaled corticosteroids in moderate-to-severe persistent asthma. The use of long-acting bronchodilator products, such as Serevent® Diskus® (salmeterol) and Foradi® (formoterol), has declined in the past year in response to concerns about an increased risk of mortality associated with these drugs in the treatment of asthma. 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 asthma controllers

Several new products will contribute to unit-cost and utilization growth for asthma controller medications over the next 3 years. Symbicort® (budesonide and formoterol), a new inhaled corticosteroid/bronchodilator combination, was introduced in mid-2007. Similar to Advair, Symbicort is administered twice daily. Two other inhaled corticosteroid/bronchodilator combinations—fluticasone/formoterol (Flutiform®) and mometasone/formoterol—are being developed for the treatment of asthma and COPD and are expected to be available in 2009. 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. Alvesco® (ciclesonide), a new inhaled corticosteroid, was approved in January 2008.
New treatments for COPD
Two long-acting beta-agonist formulations were launched in 2007 for the treatment of COPD. Bravanta® (arformoterol) and Perforomist® (formoterol) are both formulated as inhalation solutions for twice-daily administration via nebulizer. These products are similar and will compete against each other in the COPD market. Aclidinium, a new long-acting anticholinergic similar to Spiriva® (tiotropium), could reach the market in 2009.

First-time generics
Generic versions of the long-acting beta-agonist Serevent Diskus (salmeterol) may be introduced in 2008. Serevent accounted for approximately $109 million in U.S. sales in 2007.6 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 have been available for many years, but they will disappear as the market transitions from CFC-based to HFA-based inhalers by the end of 2008. The 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 the current generic albuterol inhalers (based on CFC propellants) are replaced by the 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 could 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 the costs for 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
Letairis™ (ambrisentan) is a new endothelin-A receptor antagonist that was approved in 2007 for the treatment of PAH. This agent is similar to Tracleer® (bosentan) but offers the advantage of once-daily dosing. An inhaled formulation of Remodulin® (treprostinil) that is administered via portable nebulizer is also 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. 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

First-time generics for Clarinex (desloratadine) will probably become available in 2009. However, this product may be converted to OTC status before the generic products are introduced. It is expected that the use of prescription antihistamines will decline dramatically, as it did after the OTC conversion of Claritin® (loratadine) in late 2002.

CYSTIC FIBROSIS (CF)

Several new agents may be introduced for the treatment of CF over the next few years, particularly for controlling Pseudomonas infections, which are particularly common and problematic in this disease. Aztreonam inhalation (Cayston™), an antibiotic for administration via nebulizer, is expected in 2008. 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 2009, 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. A mannitol powder inhaler is being studied as a mucolytic...
for CF patients and may also be available in 2009. Denufusol, a new drug that increases mucous hydration and clearance from the lungs, may be available in 2010.

**IDIOPATHIC PULMONARY FIBROSIS (IPF)**

Pirfenidone, an oral agent that inhibits collagen synthesis, is being developed as a treatment for IPF, a rare and serious respiratory disorder. *Actimmune®* (interferon gamma-1b) has 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 would be the first drug shown to be effective for IPF.

### Table 15. Some ambulatory-use respiratory 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>2008</td>
<td>aztreonam inhalation</td>
<td>Cystic fibrosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>montelukast + loratadine</td>
<td>Seasonal allergic rhinitis</td>
<td>$</td>
</tr>
<tr>
<td>2009</td>
<td>indacaterol</td>
<td>Asthma, COPD</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>treprostinil (inhaled)</td>
<td>Pulmonary arterial hypertension</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>fluticasone + formoterol</td>
<td>Asthma</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>aclidinium</td>
<td>COPD</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>mometasone + formoterol</td>
<td>Asthma</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>tadalafil</td>
<td>Pulmonary arterial hypertension</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>mannitol inhalation</td>
<td>Bronchiectasis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>roflumilast</td>
<td>Asthma, COPD</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>tobramycin inhalation powder</td>
<td>Cystic fibrosis</td>
<td>$</td>
</tr>
<tr>
<td>2010</td>
<td>denufusol inhalation</td>
<td>Cystic fibrosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>pirfenidone</td>
<td>Idiopathic pulmonary fibrosis</td>
<td>$$</td>
</tr>
</tbody>
</table>

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

### Oncology agents

Contribution to plan spending (2007): 3.6%  
Projected contribution to trend (2008 to 2010): 5%

#### Projected trend

Table 16. Drug trend projection for oncology agents*

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utilization increase</td>
<td>5% to 6%</td>
<td>2% to 3%</td>
<td>2% to 3%</td>
</tr>
<tr>
<td>Price and mix increase</td>
<td>6% to 7%</td>
<td>13% to 14%</td>
<td>12% to 13%</td>
</tr>
<tr>
<td>Annual total</td>
<td>11% to 13%</td>
<td>15% to 17%</td>
<td>14% to 16%</td>
</tr>
</tbody>
</table>

* Projected change in drug spending on an AWP 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

Trend driver: Oral tyrosine kinase inhibitors such as Gleevec®, Sutent®, Nexavar, and Tarceva®

Trend moderator: Erythroid stimulants such as Epogen, Procrit, and Aranesp®

More targeted drug therapies and improved biomarker testing are transforming the field of cancer treatment. According to a recent pharmaceutical report on cancer drug development, almost 650 new cancer drugs and new indications for existing cancer drugs are in clinical development. As a result, plan costs for oncology drugs, especially the more targeted and long-term oral drugs, will continue to grow briskly over the next 3 years.

CANCER TREATMENT

Treatment trends

Historically, injectable chemotherapeutic drugs for many types of cancer have been administered in short cycles because of the severe side effects associated with these medications. However, the availability of new, highly active, more targeted, and better tolerated cancer medications is causing a paradigm shift to long-term maintenance use of these therapies for many types of cancer, rather than the use of short-term cyclic treatments. Unfortunately, treatment costs will continue to increase as the new drugs are used on a long-term basis and in combination regimens that can exceed $5,000 to $10,000 for a month of treatment. 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 recent report by the National Cancer Institute, the death rates for the four most common cancers (prostate, breast, lung, and colon) are declining, as patients benefit from early detection and better treatment options.

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 multi-kinase inhibitors and oral vascular endothelial growth factor (VEGF) inhibitors. Over the next 3 years, likely drug introductions include vatalanib for colon cancer, axitinib for pancreatic and thyroid cancer, bendamustine (Treanda®) for chronic lymphocytic leukemia, and lonafarnib (Sarasar®) for breast cancer and myelodysplastic syndromes (Table 17).

SUPPORTIVE CARE

Supportive care therapies represent a significant share of the medication costs for cancer treatment. The growth rate in the use of drugs to treat neutropenia is expected to maintain 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.

On the other hand, the use of erythroid stimulants (such as Epogen, Procrit, and Aranesp) has already declined because of recent clinical evidence suggesting that these agents may be detrimental in cancer patients who are not receiving chemotherapy and that it may be harmful to elevate hemoglobin levels over 12 g/dL in either cancer or renal disease patients. As a result of these findings, the FDA has placed a black box warning on these agents.
Several new supportive care therapies could become available over the next 3 years. Mircera® (continuous erythropoietin receptor activator) received final approval in November 2007 for the treatment of anemia in patients with chronic renal failure. However, patent infringement issues are delaying availability of this drug. By 2009, Mircera may also receive approval for the treatment of chemotherapy-induced anemia. The courts will ultimately decide the timing of market availability for this drug.

Two additional new drugs, romiplostim (Nplate™) and eltrombopag (Promacta®), are being evaluated for the treatment of low platelet counts. Nplate, an injectable medication, is in clinical development for the treatment of idiopathic thrombocytopenic purpura (ITP), chemotherapy-induced thrombocytopenia (CIT), and myelodysplastic syndromes. Promacta is an investigational, once-daily oral drug that induces the proliferation and differentiation of bone marrow cells that produce platelets. An NDA has been submitted for this drug for the short-term treatment of previously treated chronic ITP. Promacta is also being evaluated for the treatment of CIT.

Table 17. 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>2008</td>
<td>axitinib</td>
<td>Pancreatic and thyroid cancer</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>bendamustine</td>
<td>Chronic lymphocytic leukemia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>vatalanib</td>
<td>Metastatic colon cancer</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>eltrombopag (Promacta®)</td>
<td>Idiopathic thrombocytopenic purpura, chemotherapy-induced thrombocytopenia (2010)</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>romiplostim</td>
<td>Idiopathic thrombocytopenic purpura, chemotherapy-induced thrombocytopenia (2010)</td>
<td>$$</td>
</tr>
<tr>
<td>2009</td>
<td>ticilimumab</td>
<td>Metastatic melanoma</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ipilimumab</td>
<td>Metastatic melanoma</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>satraplatin</td>
<td>Prostate cancer</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>enzastaurin</td>
<td>Non-Hodgkin’s lymphoma</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>$</td>
</tr>
<tr>
<td>2010</td>
<td>glufosfamide</td>
<td>Pancreatic cancer</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>epratuzumab</td>
<td>Lymphoma</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>$</td>
</tr>
<tr>
<td></td>
<td>vandetanib</td>
<td>Thyroid cancer</td>
<td>$</td>
</tr>
</tbody>
</table>

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

Treatments for age-related macular degeneration (AMD), diabetic macular edema, glaucoma, and dry eyes are the major areas of drug development for medical disorders of the eyes. The primary focus of drug development continues to be the treatment of AMD, a disorder that affects the macula (the part of the retina that is most responsible for visual acuity), and diabetic macular edema, the most common cause of vision loss in patients with diabetes. The “wet” form of AMD affects about 10% of all patients with the disease, and it is a leading cause of blindness in the elderly.77 An estimated 1.75 million American adults currently have AMD, and this number is expected to reach 3 million by 2020.78

**AGE-RELATED MACULAR DEGENERATION**

Several new drugs have already been introduced for the treatment of AMD. Lucentis® (ranibizumab) received FDA approval in June 2006 for treatment of the wet form of AMD. This drug has largely replaced Macugen® (pegaptanib) because, in addition to delaying the loss of vision, it has been shown to improve visual acuity.

Before Lucentis came to market, Avastin® had become a commonly used off-label treatment for AMD, because of the favorable experience that retinal specialists have had with the drug. Avastin is the complete antibody from which Lucentis is derived. Avastin is much less expensive to use in treating AMD because only very low doses of Avastin are required. The National Eye Institute has started a multicenter comparative study of the two drugs.79 The results, which will not be available for several years, will be of great interest to payers because of the relatively high cost of treating AMD with Lucentis.

Existing and pipeline treatments for AMD, such as afibbercept, a new VEGF-inhibiting drug, will dramatically increase utilization and costs for ophthalmological drugs. Because of the prevalence of AMD and the relatively high costs of these therapies, they will have a significant impact on the Medicare drug budget. However, these costs are likely to be borne primarily by Medicare Part B, rather than by Medicare Part D.

Table 18. Some ambulatory-use ophthalmology 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>2008</td>
<td>travoprost + timolol</td>
<td>Glaucoma</td>
<td>$</td>
</tr>
<tr>
<td>2009</td>
<td>latanoprost + timolol</td>
<td>Glaucoma</td>
<td>$</td>
</tr>
<tr>
<td>2010</td>
<td>diquafosol</td>
<td>Dry eyes</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td><strong>dexamethasone (intraocular)</strong></td>
<td>Diabetic macular edema</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>afibbercept</td>
<td>Age-related macular degeneration</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>rebamipide</td>
<td>Dry eyes</td>
<td>$</td>
</tr>
</tbody>
</table>

$ = potential to cause a $2% increase in this category’s trend.
$ = potential impact <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 trend over the next 3 years (Table 19). These include new drug treatments for bacterial and viral infections, acquired immune deficiency syndrome, overactive bladder, male and female sexual dysfunction, dermatologic diseases such as psoriasis, and numerous orphan conditions.

Table 19. 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>2008</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>olopatadine nasal spray</td>
<td>Allergic rhinitis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>17 alpha-hydroxyprogesterone injection</td>
<td>Premature labor</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>icatibant</td>
<td>Hereditary angioedema</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>C-1 esterase inhibitor</td>
<td>Hereditary angioedema</td>
<td>$</td>
</tr>
<tr>
<td>2009</td>
<td>MK-0518</td>
<td>HIV/AIDS</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>fesoterodine</td>
<td>Overactive bladder</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>lidocaine transdermal patch</td>
<td>Chronic lower back pain</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>silodosin</td>
<td>Benign prostatic hypertrophy</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>alprostadil topical gel</td>
<td>Erectile dysfunction</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>mepolizumab</td>
<td>Hypereosinophilic syndrome</td>
<td>$</td>
</tr>
<tr>
<td>2010</td>
<td>R-1626</td>
<td>Hepatitis C</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>viramidine</td>
<td>Hepatitis C</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>VX-950</td>
<td>Hepatitis C</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>eprodisate</td>
<td>Amyloid A amyloidosis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>vicriviroc</td>
<td>HIV/AIDS</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>dapoxetine</td>
<td>Premature ejaculation</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>testosterone gel</td>
<td>Female hypoactive sexual desire disorder</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>epinastine nasal spray</td>
<td>Allergic rhinitis</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>ecallantide</td>
<td>Hereditary angioedema</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>taranabant</td>
<td>Weight loss</td>
<td>$$</td>
</tr>
</tbody>
</table>

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

$ = potential impact <2% increase in this category’s trend.

Bold text indicates potential specialty drugs.
SCANNING THE HORIZON

FIVE INSIGHTS THAT WILL SHAPE HEALTHCARE
Looking toward the horizon, you can prepare for change by focusing on:

- **The forces that will redefine how healthcare is delivered and paid for.**
  The healthcare system will be transformed by changes in information technology, consumerism, benefit design, healthcare policy, and the biologic sciences. These changes will affect safety, quality, access, and cost in profound ways.

- **How to adapt your benefit design for what lies ahead.**
  New cancer vaccines, follow-on biologics, specialty drugs, behind-the-counter drugs, and biomarker tests may all require adjustments to coverage policies.

**Predictions: Emerging healthcare trends**

On July 30, 1965, the federal government enacted the Medicare program and revolutionized the American healthcare industry. Today we are on the verge of a second revolution—one that will fundamentally transform our notions of what diseases can be treated or prevented, who will be covered under our healthcare system, and how we can pay for it. Although it is difficult to predict exactly what the final outcome will be, we believe this much is certain: Five years from today, our healthcare system will cover more people, give them more and better treatment options, and deliver healthcare more efficiently than ever before.

This revolution is building momentum across five fronts:
- Information technology
- Consumerism
- Benefit design
- Healthcare policy
- Biologic sciences

This section offers a long-range view of the most powerful forces shaping the healthcare industry and how best to prepare your plan for the most likely future scenarios.
Emerging trends in information technology

“The number one benefit of information technology is that it empowers people to do what they want to do. It lets people be creative. It lets people be productive. It lets people learn things they didn't think they could learn before, and so in a sense it is all about potential.”

—Steve Ballmer, CEO, Microsoft Corporation

PREDICTION

In response to federal mandates and incentives, adoption of electronic prescribing will accelerate rapidly over the next 10 years.

Although medical technology has advanced rapidly, the healthcare industry has lagged behind other industries in incorporating information technology. Our prescribing system is still primarily paper-based. Medical records are fragmented and often difficult to share. And even though the Internet provides a wealth of healthcare information for the general public, qualitative information that people can use in making smart health-related decisions can still be hard to find.

All that is about to change. Rapid improvement in the depth, breadth, and quality of information technology in the healthcare industry will provide a major impetus. Spurred on by new legislation, electronic prescribing (e-prescribing) will begin to fulfill its promise of improving patient safety and increasing efficiency on a wide scale. Applications for integrated medical, pharmacy, lab, and self-reported health data will expand rapidly. The power of information sharing will propel the healthcare sector into a leadership position in the use of information technology.

ELECTRONIC PRESCRIBING

Improving efficiency. Promoting adoption.

Key insights
- E-prescribing will be a key element in improving patient safety and reducing healthcare costs.
- New federal legislation is likely to accelerate adoption of e-prescribing systems.

The current paper-based system of prescribing medication raises concerns about safety and efficiency. In a 2007 report to Congress, experts predicted that a nationwide shift to e-prescribing could prevent over 2 million adverse drug events, 130,000 of them life-threatening.¹ A recent review of several studies by researchers at the University of Minnesota concluded that illegible handwriting and transcription errors account for 60% of medication errors.² They also found that medication errors can be reduced by up to 66% in hospitals that switch to an e-prescribing system. Hospitals spend up to $5.6 million per year for adverse events that are caused by medication errors, so the potential savings from reducing these errors are substantial.³

In addition to reducing the human and financial cost of medication errors, e-prescribing systems can help achieve savings by helping doctors make more informed choices when selecting drugs. These systems alert physicians to potential drug interactions and a variety of other pertinent information before they make their prescribing decisions. According to the Centers for Medicare and Medicaid Services (CMS), adoption of e-prescribing would save an estimated $2.7 billion annually just by enabling physicians to reduce the time they spend on the phone clarifying and correcting prescription information. CMS reports that, overall, widespread adoption of e-prescribing could save the U.S. healthcare system $27 billion per year.³
In spite of the evidence supporting the benefits of e-prescribing systems, their adoption remains limited. Fewer than 10% of U.S. physicians use e-prescribing technology in their practices. Barriers to adoption include the potential disruption of physician office workflow, the lack of standards for interoperability (which would allow competing systems to share information effectively), the cost of the systems, and concern about regulations that prohibit the electronic transmission of prescriptions for controlled substances.

Progress on the legislative front
Recognizing the potential of e-prescribing systems, Congress mandated the establishment of national e-prescribing standards as part of the legislation that created the Medicare Part D prescription drug benefit. Although the legislation falls short of requiring prescribers to write prescriptions electronically, it does specify that all who do so must follow a defined set of standards. All Medicare Part D sponsors must support and comply with e-prescribing standards when communicating with prescribers who use e-prescribing technology. Pharmacists who receive electronic prescriptions are required to accept electronic prescriptions for Medicare members.

New legislation has been introduced to mandate the use of e-prescribing in certain settings. In December 2007, Senator John Kerry introduced a bill that would require physicians who treat Medicare-covered patients to use e-prescribing by January 1, 2011. The bill, which offers strong incentives, including reimbursements for purchasing some of the needed hardware and software, has received strong bipartisan support but remains in committee as of this writing.

Meanwhile, other legislative and regulatory initiatives may remove additional barriers. For example, industry groups have challenged the Drug Enforcement Administration's requirement that prescriptions for controlled substances not be transmitted electronically. That regulation, which in effect forces physicians who wish to use e-prescribing to maintain two systems, is cited as one of the primary reasons why doctors do not adopt the systems.

Given the broad congressional support for legislation to encourage the use of e-prescribing systems, it is highly likely that significant progress will be made in the near future toward reaching that goal.

How to prepare your plan for the future
- Provide a checklist to assist prescribers in evaluating and selecting e-prescribing systems.
- Encourage high-volume prescribers to adopt e-prescribing systems, providing them with incentives where you can.
- Lobby for passage of legislation favorable to e-prescribing.

CASE STUDY: DEMONSTRATING THE VALUE OF E-PRESCRIBING
In February 2005, the three major American automakers, their insurers, and Medco joined forces to launch the Southeast Michigan e-Prescribing Initiative (SEMI), a pilot program that offered physicians financial incentives to adopt e-prescribing systems. The pilot program enjoyed considerable early success:
- Formulary compliance improved 2%.
- Calls from pharmacists were reduced by 87.2 calls per 1,000 prescriptions.
- Savings were estimated at $9,247 per prescribing physician.

The SEMI program has built on these achievements over the past year. The program has more than doubled in size, with over 300,000 physicians now participating. More than 75 million electronic prescriptions have been transmitted since the program’s inception, a number that grows by over 300,000 per month.
In January 2008, the SEMI partners conducted a survey of 500 participating physician offices to assess doctors’ views of the program. Overall, the results were highly positive:

- 90% of the surveyed physicians reported that e-prescribing met or exceeded their expectations.
- 75% strongly agreed that e-prescribing improves patient safety.
- Almost 70% strongly agreed that e-prescribing improves the quality of patient care.
- 65% said they had changed at least one prescription because of a safety alert.
- 72% reported a reduction in communications from pharmacists.

An analysis of prescription claims provided further demonstration that e-prescribing has a positive impact on patient safety and formulary compliance. A review of 3.3 million electronic prescriptions revealed several favorable impacts on physician prescribing:

- A severe or moderate drug-drug interaction alert was sent to physicians for more than 1 million prescriptions. Nearly 423,000 (41%) of these prescriptions were changed or canceled by the prescribing physician.
- More than 100,000 medication allergy alerts were presented. Physicians acted on more than 41,000 (41%) of these alerts.
- When formulary alerts were presented, physicians changed the prescription to comply with formulary requirements 39% of the time.

The SEMI results indicate that physicians who are given incentives to adopt e-prescribing systems have an overwhelmingly positive attitude toward them and that measurable improvement can be made in the safety, efficiency, and cost-effectiveness of prescribing practices.

**INTEGRATED DATA**

*Combining data. Coordinating care.*

**Key insights**

- The lack of integrated data can sometimes lead to counterproductive or even dangerous combinations of therapies.
- Integrated data will help improve health and cost outcomes, and power a new generation of coordinated care services.

The growing complexity of healthcare delivery challenges our ability to provide sound, coordinated care. The medication that one physician prescribes for a patient may interfere with a medication prescribed by another. A disease management nurse may offer advice that differs from that of the patient’s pharmacist, which in turn may run contrary to the directions given by a doctor or dietitian. Those who pay for healthcare may have little assurance that medical care for a given diagnosis is coordinated with pharmacy care or that information is relayed to the patient in a way he or she can understand and follow. This problem exists not necessarily because of lack of concern or skill on the part of healthcare professionals, but because they each have an incomplete view of a patient’s care plan. Integrated data can help address these issues.

*Integrated data* refers to the linking, organizing, and enhancing of patient-specific medical, pharmacy, lab, and self-reported health data. Integrated data programs provide a comprehensive view of the healthcare services that an individual patient or a specific population has received. The practical applications of integrated data are increasingly diverse and rapidly expanding.
At the simplest level, integrated data programs help healthcare providers ensure that a given intervention is neither dangerous nor counterproductive as part of a regimen. These programs can identify situations in which patients who are taking certain medications are not receiving adequate supervision or in which patients with certain diagnoses are not receiving proper medication. Integrated data can also be used across an entire population of patients to identify those in need of additional care. By distilling the essence of a patient’s conditions and treatments, integrated data programs give the provider a simple, clear picture of how the patient’s diseases are progressing, recurring, and interacting.

Medco clients have embraced integrated data programs like RationalMed® at a rapid rate. At the end of 2007, 28.9% of Medco members were protected by this program, an increase of 44% from the end of 2005. Medco’s new integrated data program, RationalIQ™, can be used to screen entire patient populations for harmful or inappropriate combinations of medical treatment and prescription drug therapies.

### How to prepare your plan for the future

- Assess the ability of your healthcare vendors to transfer and integrate patient-specific information that can help coordinate care.
- Talk with your vendors about integrated data screening programs to help identify opportunities for improving the type of care your members receive.
- Use integrated data initially in the areas with the highest plan spending or disease prevalence, or with the most significant gaps in care.

### CASE STUDY: IDENTIFYING UNSUPERVISED USE OF ANTIPSYCHOTICS

A large national employer was experiencing high medical and pharmacy costs for the treatment of patients with schizoaffective disorder. The client wanted to understand what was driving these costs, so that the overall costs of care could be managed more effectively.

To help identify the possible causes of the higher costs, Medco conducted an integrated analysis of medical and pharmacy claims data on the client’s behalf. The analysis followed procedures based on the Health Insurance Portability and Accountability Act (HIPAA) and other regulations for the protection of individual health information and patient privacy.

The analysis revealed that a significant portion of medications used by patients with schizoaffective disorder were being prescribed without proper clinical oversight. More than 20% of antipsychotic drug prescriptions and almost 30% of antidepressant drug prescriptions were not associated with a related office visit. Schizoaffective disorder requires close oversight to ensure effective dosing, monitor for noncompliance, and avoid significant and even dangerous side effects.

The integrated data review also revealed that hospital readmission rates for patients who were not receiving adequate medical supervision were approximately 15% higher than the clinical benchmark. The benefit plan was incurring significant incremental costs for hospital visits in the unsupervised population. Readmissions were responsible for 63% of the employer’s total hospital costs for patients with schizoaffective disorder.

Suspected cases of inadequate medication supervision were assigned to a mental health vendor for follow-up and additional monitoring.
Emerging trends in consumerism

“Actionable information, interactivity and communications to better manage consumer behavior will be a leading spend category for healthcare plans through 2010.”

—Janice Young, Director, Health Industry Insights

PREDICTION

Although the future of consumer-directed health (CDH) plans is uncertain, healthcare consumerism in the broad sense will become an increasingly powerful force as personal access to healthcare information expands.

Consumerism is a growing force within the healthcare industry. Although many gaps still need to be addressed, more people are gaining access to the information they need to make better healthcare decisions. Increasingly, that information comes from not only the medical community but also social networks of patients sharing their experiences with one another. Advances in systems that simplify the keeping and sharing of personal health records will further empower consumers to take more direct control of their healthcare decisions.

Initial efforts to incorporate consumerism into benefit design have met with limited success. Benefit plan members have been reluctant to select new forms of healthcare coverage that make them more responsible for how their healthcare dollars are spent. A rapidly increasing number of payers now offer a CDH plan option, which typically includes a high deductible for medical and pharmacy expenses. However, member enrollment has not kept pace with the availability of these plans. Across Medco’s book of business, only 2.6 million members—fewer than 5%—have enrolled in the CDH plans offered by its clients. Also, most plan sponsors have not experienced the dramatic improvements in healthcare purchasing decisions that these plans are designed to foster. Use of mail order is only 1.2% higher for members with CDH plans, and generic dispensing rates for mail-order prescriptions are only 1% higher.

An increasing number of plan sponsors are incorporating deductibles into their prescription benefit plans. Historically, the vast majority of these plans have not included deductibles for prescription drug purchases. However, over the past 3 years, there has been a dramatic increase in the use of deductibles in pharmacy plan designs (Figure 1). One objective of the new deductibles is to create incentives for plan members to make cost-effective choices and take greater financial responsibility for their prescription benefits. During the same time period, there has also been a dramatic increase in the number of plans with annual out-of-pocket maximums for prescription drug purchases. This feature is similar to the catastrophic phase of the Medicare Part D benefit, and it demonstrates a growing interest in limiting members’ overall financial risk for prescription drug costs.

Figure 1. Plan designs that include a deductible or out-of-pocket maximum
Source: Medco data

Note: The figure shows the percentage of members who participate in a prescription benefit plan that includes a deductible or an annual out-of-pocket maximum.
**SOCIAL NETWORKING**

*Immediate impact. Growing importance.*

**Key insights**

- Social networks will increasingly influence healthcare-related purchasing decisions.
- Consumers should be cautioned that healthcare information provided through social networks is not necessarily accurate and that peer-to-peer advice on health matters varies in reliability.

The same dynamics that have transformed everything from popular music to investment advice to dating are beginning to change how consumers obtain information about health and healthcare professionals. An increasing number of consumers now turn to a rapidly growing number of online social networking communities for both professional and peer recommendations about a broad spectrum of health matters.

Once mere repositories of static health information, health-oriented websites are developing blogs, podcasts, and specialized search engines to deliver timely information on health-related subjects. Leading sites such as WebMD and RevolutionHealth host message boards, blogs, and chat rooms on literally hundreds of healthcare topics. Patients have formed active user groups on virtually every major condition and created boards on an astonishing range of topics.

The methodologies pioneered by private-sector websites enable advocacy groups, government agencies, and healthcare professionals to deliver relevant news and personalized health-awareness messages. Both the American Cancer Society (www.cancer.org) and the Centers for Disease Control and Prevention (www.cdc.gov), for example, have been experimenting with various forms of online communities to test whether they can help spread the word about such topics as nutrition, cancer screening, and infectious disease prevention.9

As healthcare consumers increasingly turn to one another for health advice, important issues about credibility will arise. As with any public forum, consumers will receive solid advice mixed with conjecture and erroneous information. Some consideration should be given to providing plan members with reliable sources of information that they can use to verify the information they accumulate through networking forums.

**How to prepare your plan for the future**

- Lobby for legislation that mandates the reporting of physician performance and price information.
- Consider providing resources to help plan members access social communities through portals that balance the advice of peers with the wisdom of experts.

**HEALTH LITERACY**

*Deeper understanding. Better results.*

**Key insight**

- Healthcare communications are more effective when based on accurate assessments of the audience's health literacy.
If Americans are to make better health and healthcare purchasing decisions, they will need to understand and act on health information that is relevant to their conditions. Addressing these needs requires two important parallel efforts. Health communications must be based on an accurate assessment of what various audiences already know and are capable of understanding, and efforts must be made to expand that base of knowledge, particularly in communities in which the lack of health knowledge has contributed to relatively poor outcomes.

Health literacy initiatives seek to understand and improve how patients comprehend healthcare information and advice. Early studies indicate that there is a pressing need for these initiatives. A report by the Institute of Medicine estimates that 90 million American adults have difficulty understanding and using health information. Limited health literacy has been associated with a high rate of hospitalization and increased use of emergency services, amounting to billions of dollars in avoidable healthcare costs.

A pervasive problem
Although concerns about health literacy touch all aspects of American society, communication barriers are especially prevalent among low-income minority populations. For example, Americans with lower socioeconomic status and low health literacy are less likely to be screened for cancer and more likely to have advanced cancer at diagnosis. According to the American Medical Association, patients who may be most at risk for ineffective communication include those who speak limited or no English and those from minority cultural groups who may not share “mainstream” health beliefs and values.

Looking forward, it is likely that programs designed to improve the health literacy of Americans will steadily expand and that broad measures of health literacy will improve.

How to prepare your plan for the future
- Consider surveying your membership to assess current levels of health literacy.
- Adjust health-related communications to appropriate literacy levels by getting direct input from those who will be using them.
- Assess the cultural and language barriers particular to your membership before developing content or having materials translated into other languages.

PERSONAL HEALTH RECORDS

Key insights
- Electronic health records offer great promise for increasing efficiency and reducing medical errors.
- Substantial progress is being made to ensure the interoperability of personal health records.

The term personal health record (PHR) has been used for at least 30 years, referring first to the paper files kept by people about their own health and medical treatment. In the modern context, however, PHR refers to the rapidly growing number of computer-based tools to gather, store, and share personal health and medical data.
There is a difference between PHRs and electronic health records (EHRs). EHRs are the systems that healthcare providers use to store and share medical records. These include all the efforts to convert patients’ medical charts from paper to digital files. Claim-based records, which are not technically medical or health records, are also considered to be EHRs. Electronic records are growing in popularity because they provide a reasonably comprehensive view of a patient’s treatment history and can be more easily created and maintained by the patient’s employer or health plan.

Although PHRs often use electronic systems, they contain health information that is under patients’ control, enabling them to keep it or share it as they wish. Depending on the system and the desires of the patient, the amount and nature of data stored as a PHR vary widely. Typically a PHR includes some information about:

- Allergies, including adverse drug reactions
- Prescription medications
- Over-the-counter (OTC) and herbal medications
- Illnesses and hospitalizations
- Surgeries and other procedures
- Vaccinations
- Laboratory test results
- Family history

Well over 100 vendors—from software manufacturers to insurance companies to websites—offer PHR systems. The programs range from simple electronic diaries to more comprehensive suites that link directly with doctors or hospitals for direct downloading of electronic charts. Depending on the system, the data may be stored on the patient’s home computer, the vendor’s server, or some sort of portable storage device. Several paper-based systems are also still available.

Given the vast number of competitors in this new market, concerns have been raised about the interoperability of all these systems. Recently, two large insurance trade groups released a model for PHRs with the hope of creating a broad standard for what these systems should contain and how they should share data. The model includes definitions of data elements that should be included, standards of PHR portability between insurers and providers, and rules about when insurers can share the information.

Viewed as an effective way to reduce medical errors and increase efficiency, EHRs enjoy great support across the medical, insurance, and political communities. President Bush has called for all Americans to have EHRs and PHRs by 2014—a goal that has strong bipartisan support in Congress. With such a strong tailwind, it is likely that PHRs will be adopted rapidly in the coming years.

**How to prepare your plan for the future**

- Encourage your members to initiate and maintain PHRs.
- When evaluating PHR vendors, consider portability, so that the investment is not lost if a member switches health plans.
- Consider “smart PHR” vendors that use data to coach members to higher levels of care.
Emerging trends in benefit design

“Current health insurance benefit designs that simply rely on higher, one-size-fits-all patient cost sharing have limited potential to curb rapidly rising costs, but innovations in benefit design can potentially make cost sharing a more effective tool. Innovative benefit designs include incentives to encourage healthy behaviors; incentives that vary by service type, patient condition or enrollee income; and incentives to use efficient providers.”

—Center for Studying Health System Change

PREDICTION

Generic dispensing rates will increase rapidly as patents on blockbuster medications expire and plan sponsors become more savvy about how to capitalize on the availability of new generics.

As the healthcare market continues to evolve, benefit design must keep pace. New metrics and strategies are being introduced to provide plans with tools for understanding and managing their expenditures. These tools, in combination with a steady stream of blockbuster medications coming off patent, will fuel rapid growth in the utilization of generic drugs. Biosimilar drugs (follow-on biologics) are not likely to make any meaningful inroads into the American market for at least the next few years. Their eventual emergence, however, will raise additional challenges for the design of specialty pharmacy coverage.

Medical and pharmacy benefit plan designs will need to be modified over the next few years to take several market trends into account: the growing availability and use of generic medications, the increasing use of specialty drugs, and the use of OTC products as add-on therapies in pharmaceutical care.

GENERIC PERFORMANCE METRICS

New measures. New opportunity.

Key insights
- Generic alternatives, not generic equivalents, account for most of the opportunities available to plans to achieve savings through the use of generics.
- A new performance metric, the Generic Opportunity Score, helps define the potential for using generic alternatives to achieve plan and member savings.

Traditionally, two metrics have been used to measure generic utilization: generic substitution rate (GSR) and generic dispensing rate (GDR):
- GSR measures the percentage of prescriptions that are dispensed as generics when generic equivalents are available for a brand-name drug. Generic equivalents are medications that have the same active ingredient as the brand-name drug. GSR can be as high as 100% if all of the opportunities for generic substitution (dispensing the generic equivalent) are realized.
- GDR measures the percentage of all prescriptions that are dispensed as generics. Achieving a GDR of 100% is not a practical goal because single-source brand-name drugs are the only available option in some therapeutic areas. The average GDR for Medco clients in 2007 was 59.7%.

Although both GSR and GDR have proven to be useful metrics, they do not provide insight into a plan’s total potential for increasing generic utilization through the use of generic equivalents and generic alternatives. Generic alternatives are
generic drugs that contain different active ingredients but usually provide a similar effect when given in place of a brand-name medication in the same or a similar therapeutic class.

A new metric
To meet the need for a more comprehensive and actionable measure of generic performance, Medco has created a new metric called the Generic Opportunity Score (GOS).* GOS is the percentage of prescriptions that are dispensed as generics 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. GOS can be as high as 100% if all of the potential opportunities for generic equivalents and alternatives are utilized.

GOS is determined from a clinical assessment of the opportunities to use generic alternatives for selected brand-name medications, taking similarity of indications, efficacy, and safety into account. This assessment is adjusted to reflect the likelihood that patients could be treated with the generic alternative in clinical practice, based on an assessment of published research and clinical evidence. The adjusted assessment defines the opportunity for using generic alternatives.

Taking action
For plan sponsors, GOS measures how well they are using generics today relative to the total opportunity, and it also highlights how much opportunity remains. In almost all cases, the bulk of the remaining generics opportunity is through the use of generic alternatives, not generic equivalents.

The differences in how GDR, GSR, and GOS measure generic utilization are illustrated in Figure 2 for a typical plan.

- GDR measures generic utilization relative to all dispensing. In this example, 59.7% of all prescriptions were dispensed as generics.
- GSR measures generic utilization relative to the dispensing of brands that have generic equivalents. In this example, 96.3% of prescriptions were dispensed using generic equivalents when the opportunity was available. The remaining 3.7% represents missed opportunities for generic substitution.
- GOS measures generic utilization relative to the dispensing of brands that have either generic equivalents or generic alternatives. In this example, 78.5% of prescriptions were dispensed as generics when the opportunity to use a generic equivalent or a generic alternative was available. The remaining 21.5% represents missed opportunities for using generic equivalents or generic alternatives.

*Patent pending

Figure 2. Measures of generic dispensing performance and opportunity
Source: Medco data

Note: The figure illustrates three ways of measuring current generic dispensing and the opportunities for increased generic dispensing in a typical benefit plan. In this example, GSR is 96.3% of the opportunity for brands with equivalents, GOS is 78.5% of the opportunity for brands with equivalents and alternatives, and GDR is 59.7% of all prescriptions.
An analysis of overall generic performance (as illustrated in Figure 2) is the starting point for identifying more targeted opportunities for action. Once the overall opportunity is identified, estimates can be made about the potential savings based on plan-specific pricing for all generic opportunities or for the therapeutic classes that show the greatest potential. Figure 3 displays a savings analysis for a typical plan. For this plan, 95% of the savings opportunity is associated with generic alternatives and 5% with generic equivalents. Most of the opportunity for generic alternatives is concentrated in five therapeutic classes—lipid-lowering drugs, antihypertensives, psychotherapeutic drugs, ulcer and heartburn drugs, and treatments for benign prostatic hypertrophy (BPH).

A detailed analysis of generic opportunities enables plans to focus their strategies to encourage greater use of generics, both equivalents and alternatives, in targeted therapeutic classes.

**How to prepare your plan for the future**
- Employ metrics such as GOS to identify generic savings opportunities.
- Consider adjusting your generics strategy to address high-value opportunities within specific drug classes.

**CASE STUDY: PRESERVING A GENEROUS PRESCRIPTION BENEFIT**

A large labor union operated under the philosophy that any prescription therapy their members required should be either free or very inexpensive. As costs rose, the plan implemented an inventive custom formulary to preserve a generous benefit.

The union had historically covered generics and formulary brand-name medications for its members without any co-payment. To help preserve this benefit over the years, the plan had implemented penalty co-payments of $4 to $16 for select categories of nonpreferred brands and a retail refill allowance program to encourage use of mail-order dispensing. The plan was willing to limit choice in order to maintain the $0 co-payment option.

**Actions**
Medco worked with the union’s staff, including three staff pharmacists and the communications and operations teams, to design a custom formulary and a robust member communication and education program. Medco and the client worked together to narrow the formulary in several therapeutic classes to focus on generics, and they collectively negotiated aggressive rebates with preferred-brand drug manufacturers. The targeted classes represented approximately 45% of the client’s total drug spending.

The plan changes were communicated through a variety of channels. Wallet guides with the new formulary were issued to members. A pharmacist call program was set up to assist with formulary interchanges. The client and Medco supplemented an existing joint customer service capability and on-site prior authorization program with additional training and support. Finally, the top 500 prescribing physicians were notified by fax of the formulary changes.
Outcomes
The custom formulary achieved strong savings for the plan. Across all categories, the generic dispensing rate jumped approximately 6% in the first quarter after the program was implemented, and plan spending is expected to decrease at an annual rate of 8% to 10%. Beyond the anticipated savings, the union felt that the program was the right thing to do for its members, preserving a $0 co-payment choice for the foreseeable future.

SPECIALTY PLAN DESIGN

Pharmacy benefit, medical benefit, or new benefit?

Key insights
- Traditional pharmacy and medical benefit design and distribution models do not fully manage the unique requirements and characteristics of specialty drugs.
- Plans can develop hybrid benefit designs that specifically manage specialty drugs and associated patient care.

Specialty drugs are currently managed under the pharmacy benefit, the medical benefit, and sometimes both. These drugs have varied and unique requirements that make them difficult to manage exclusively under either benefit:
- Some specialty drugs are self-administered, while others require administration by a healthcare professional.
- Many specialty drugs require administration supplies and services.
- Specialty drugs may be supplied by a specialty pharmacy, the prescribing physician, an infusion center, or a home healthcare organization.
- Specialty patients benefit from clinical and therapy management support services.

Same drug, different out-of-pocket costs
Allowing the same specialty drug to be covered under both the medical and pharmacy benefit can lead to considerable discrepancies in member cost share. For example, under typical benefit plan coverage, the patient cost share for a $2,000 prescription might range from $0 to $400:
- Pharmacy benefit co-payment = $50
- Medical benefit coinsurance (20%) before maximum out-of-pocket is reached = $400
- Medical benefit coinsurance (0%) after maximum out-of-pocket is reached = $0
- Medical benefit when drug is included in physician office co-payment = $15

These cost-share differences may have unintended consequences. They could encourage the use of more costly locations for drug administration or the use of more costly infused therapies instead of self-administered medications. With traditional drugs there is no financial incentive for the prescriber to select one therapy over another. A prescription is written by a physician and dispensed by a pharmacy. However, when the physician is both the prescriber and the retailer of specialty drugs, an incentive may be created for the physician to select a drug that he or she retails at a profit.

As members move between benefits to obtain the lowest cost share, important health and safety issues may be compromised. In most cases, drug utilization review (DUR) can occur only when the drug is dispensed under the pharmacy benefit, where it is managed by a product-specific National Drug Code (NDC). Drugs billed under the medical benefit, using far less precise billing codes, are not generally subject to DUR and health and safety reviews.

Lack of precision in billing specialty medications under the medical benefit can also hinder efforts to implement rules and criteria for the coverage of specialty drugs under the provisions of a given plan. Drugs billed under the medical benefit may inadvertently create a “back door” that allows members to obtain coverage of a specialty drug that was not intended by the plan.
A new model for specialty benefits
In the near future, forward-thinking plans will develop hybrid benefit designs that focus specifically on managing specialty drugs and associated services. All specialty drugs will be consolidated into a single benefit and managed at the NDC level. The new benefit design will include a unified cost-share strategy and uniform coverage rules. Drugs will be supplied using the most cost-effective and clinically appropriate mode of distribution. All drugs will receive the same level of health and safety monitoring, and all patients will receive the appropriate supplies and therapy management services. Plans will aggregate their specialty volume to obtain the best discounts, and they will focus on clinical outcomes to eliminate unnecessary medical costs. These hybrid plans will be designed to maximize the value of biosimilar products as they become available and to leverage the predictive capabilities of personalized medicine.

Under the current split coverage system, it can be difficult to capture a complete view of a patient’s medications. Pharmacists who are performing DUR for patients’ traditional prescription drugs may have little to no knowledge of any specialty drugs the patients are taking, especially if those drugs are infused or billed under the medical benefit. This situation could compromise patient safety by failing to account for potential drug interactions. A hybrid specialty platform could support more effective DUR screening by tracking a patient’s full range of medications.

As the specialty medication category grows broader, financial issues will grow more complex. More competition within therapeutic classes, yielding better cost-management opportunities (particularly when biosimilar drugs enter the market) will play to the traditional strengths of the pharmaceutical benefit. However, many of these therapies will also carry infusion charges, nursing fees, and other costs traditionally assigned to the medical benefit. A growing number of specialty drugs come with companion genetic tests, raising questions about whether testing should be billed under one benefit and medications under another. A hybrid specialty platform could help clarify these issues by accommodating both the medical and the pharmacy components of a patient’s specialty drug treatments.

The growing cost and complexity of specialty medications is likely to add some urgency to this matter. Specialty drugs now account for 11.4% of drugs billed through the pharmacy benefit. A new coverage structure may be needed to more effectively manage the growing number of patients who are becoming eligible for these expensive medications.

How to prepare your plan for the future
- As new specialty drugs are approved, consider whether they are best covered under the medical or pharmacy benefit, and determine coverage provisions up front.
- Evaluate the financial and clinical benefits of developing a hybrid benefit design focused specifically on managing specialty drugs.
- Determine whether your plan can save money by transferring specialty medications from the medical to the pharmacy benefit.

CASE STUDY: OPTIMIZING THE SPECIALTY DRUG BENEFIT
A large national employer provided coverage for specialty medications through a combination of its pharmacy benefit and its medical benefit, which included four distinct medical plans. A RationalMed analysis of specialty drug spending raised concerns that coverage under the various benefit plans made it difficult to measure and manage specialty spending and created inconsistencies in coverage criteria.

The employer wanted to gain better control over spending for specialty drugs billed under the medical benefit. The employer also wanted to capitalize on the coverage rules, utilization review, and favorable pricing available through a preferred specialty pharmacy.
**Actions**
The employer worked with Medco and four medical carriers to implement a series of changes to its coverage rules. The initiative began by moving all self-administrable and rare-disease specialty medications from the medical benefit to the pharmacy benefit. The objective was to cover specialty drugs solely under the pharmacy benefit and distribute them through a preferred specialty pharmacy.

Current patients were notified in advance of the coverage change via letters and phone calls. Key physicians and care management providers were also notified of the rule change in advance of implementation. A pay-and-educate program was established to ease the transition. This coupled coverage for one fill under the medical benefit with a final notification that future fills would be covered only under the pharmacy benefit.

**Outcomes**
- The coverage changes proceeded with virtually no member complaints. The combination of clear communications and the pay-and-educate program made a compelling case for the rule change, demonstrating the importance of effective communication before plan implementation.
- Plan spending for self-administrable and rare-disease specialty medications has gained visibility and is being managed more effectively.
- Utilization has declined in some therapeutic classes (such as growth hormones), suggesting that coverage review under the pharmacy benefit has had the effect of discouraging inappropriate utilization.

**ADJUNCT THERAPY WITH OTC DRUGS**

**New treatment options. New coverage rules.**

**Key insight**
- Pharmacy benefit coverage may need to expand to include OTC drugs that are used as adjunct therapies.

An adjunct therapy, also known as an add-on therapy, is a supplemental medication used with a primary treatment in order to achieve an improved clinical outcome. Adjunct therapies are used in the treatment of many diseases and typically involve combinations of prescription drugs. In recent studies, however, certain OTC medications have demonstrated efficacy as adjunct therapies. These include OTCs used with statins to reduce triglyceride levels and, in some instances, aspirin used as an adjunct to the blood thinner warfarin.

Some of the most encouraging results come from a 2007 study that compared therapy regimens in the eradication of *Helicobacter pylori* infection, which has been linked to peptic ulcers and gastric cancer. Treatment of *H. pylori* infection usually consists of a combination of two or three antibiotics and a proton pump inhibitor. This regimen has proven to be 80% effective after 10 days of treatment. The recent study compared a group who took the traditional regimen with a group who took the traditional regimen combined with two OTC therapies, lactoferrin (a milk protein that binds iron) and a probiotic. *H. pylori* was eradicated in 72.5% of the group who took the traditional regimen and in 88.6% of the group who received the adjunct therapies. Achieving this dramatic improvement in outcome entails only modest additional cost because both OTC drugs are relatively inexpensive.

**How to prepare your plan for the future**
- Consider covering certain drugs as adjunct therapies, particularly those that show dramatic results in improving the efficacy of prescription medications.
- Determine how claims for OTC medications can be processed through the pharmacy benefit for both retail and mail-order purchases.
Emerging trends in healthcare policy

“I am concerned about the whole man. I am concerned about what the people, using their government as an instrument and a tool, can do toward building the whole man, which will mean a better society and a better world.”
—Lyndon B. Johnson, President of the United States, upon signing the Medicare Bill of 1965

PREDICTION

Over the next 5 years, a federal framework will be developed to cover all or most of the Americans who have no health insurance coverage.

The federal government is adopting a more aggressive posture in driving changes in the American healthcare system. One of the most pressing healthcare problems that Congress must address is the lack of health insurance for millions of adults and children in the United States. How this situation should be rectified continues to be hotly debated, but there is widespread acceptance that the status quo is both ethically and economically untenable.

The federal government is also working toward establishing a pathway for the approval of biosimilar drugs, which are also referred to as follow-on biologics or biogenerics. Legislation is likely to be enacted in the next few years, but the impact is difficult to gauge because specific provisions are still being developed.

As discussed earlier, CMS and Congress are both pursuing initiatives to increase the use of e-prescribing systems. CMS is also taking measures to increase accountability based on quality measures, especially within Medicare Part D. The FDA, meanwhile, is actively considering a new category of behind-the-counter drugs that would require a pharmacist’s consultation but not a prescription.

HEALTHCARE COVERAGE FOR THE UNINSURED

47 million uninsured Americans can’t be right.

Key insight

- Healthcare coverage for the large number of Americans without insurance will be an important issue in the upcoming presidential elections and a legislative priority in the next Congress.

More than 47 million Americans, approximately one in seven, currently have no health insurance. Every year, the United States spends nearly $100 billion to provide healthcare for uninsured patients, often for conditions that could have been prevented or more efficiently treated with earlier diagnosis. Of course, these costs must somehow be borne by the rest of the system. A 2005 study found that the cost-shifting added 8.5% to the average health insurance premium.

Who are the uninsured?

Although the total number of uninsured Americans is widely quoted, the nature of that population is generally less well known. Uninsured Americans represent a broad demographic and economic cross-section of U.S. residents. Few of the uninsured are over age 65, because of Medicare, and few of the very poorest are uninsured, because they qualify for Medicaid. A total of 8.5 million of the uninsured are children, comprising 18% of the total. Nearly 80% of all uninsured Americans are from families in which at least one adult in the household has a job. More than 31% of uninsured Americans are from families with annual household incomes over $50,000 (Table 1).
Strategies for covering the uninsured

Over the past year, presidential candidates, elected officials, and various organizations have proposed strategies for providing some type of healthcare coverage, or increased access to coverage, for uninsured Americans. The majority of plans focus on one or a combination of four basic approaches:

1. Expanding existing programs
2. Creating a new government health insurance plan
3. Changing the tax code to provide incentives for people to purchase private insurance
4. Mandating coverage for all or some subset of Americans

Expanding access

There is ongoing debate in Congress about whether existing federal and state programs such as the State Children’s Health Insurance Program (SCHIP) and Medicaid should be expanded to cover more individuals. SCHIP currently provides coverage to about 6.7 million people, and interest has been shown in expanding this program to cover an additional 4 million people by 2012. Some argue that additional funding for these programs would provide access to those who can least afford it. Opponents of increased funding argue that it would increase the federal deficit and potentially lead toward a single federal payer system. Opponents also note that many people currently eligible for Medicaid or SCHIP are not enrolled and that they should be enrolled before any expansion is considered. Finally, opponents are concerned that increasing or expanding federal programs like SCHIP will “crowd out” the private-based insurance market. The debate over the expansion of Medicaid and SCHIP will very likely continue after the presidential elections in November.

New federal program

Some candidates and lawmakers have suggested that a new federal program be created, one modeled after Medicare or the Federal Employees Health Benefit Plan, as a way to provide coverage to the uninsured. Although cost estimates for such plans are high, proponents argue that they would drastically reduce, if not eliminate, the number of uninsured Americans. The details of such proposals have not been fleshed out and face increasing scrutiny in today’s economic climate. Still, the idea of a newly created federal program continues to garner attention.

Tax changes

Many proposals include a call for the federal government to subsidize the purchase of private health insurance, particularly for lower-income individuals who do not qualify for Medicaid. The AMA has called for individual premiums to be made tax-deductible, similar to employer premiums. President Bush and at least one presidential candidate have proposed providing a tax credit to people who purchase healthcare insurance for themselves and their families in the private market. Many believe that such a credit would need to be payable as a rebate, given that many uninsured people do not have any tax liability. Opponents point out that many uninsured Americans might choose to spend their limited income on housing and other basic needs, foregoing health insurance. Proponents note that nearly 5 million uninsured households have incomes over $75,000. They suggest that a tax credit would entice middle-income families to purchase coverage in the private market, particularly those who don’t have access to employer-based coverage.

---

Table 1. Demographics of uninsured Americans
Source: U.S. Census Bureau

<table>
<thead>
<tr>
<th>Age distribution</th>
<th>Uninsured (%)</th>
<th>Family income</th>
<th>Uninsured (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 18</td>
<td>18%</td>
<td>Less than $25,000</td>
<td>39%</td>
</tr>
<tr>
<td>18 to 24</td>
<td>18%</td>
<td>$25,000 to $49,999</td>
<td>31%</td>
</tr>
<tr>
<td>25 to 34</td>
<td>23%</td>
<td>$50,000 to $74,999</td>
<td>15%</td>
</tr>
<tr>
<td>35 to 44</td>
<td>17%</td>
<td>$75,000 or more</td>
<td>16%</td>
</tr>
<tr>
<td>45 to 54</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over 55</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Mandatory coverage**

A number of states (notably California and Massachusetts) and even a few municipalities have passed legislation aimed at providing universal healthcare coverage for their residents. Generally, these laws require uninsured residents to purchase healthcare insurance or employers to provide it. The Massachusetts program includes fines for residents who fail to obtain coverage. In the first year of this program, the fines were set at a relatively modest $219. However, they could rise to as much as $912 for some residents this year. To date, the Massachusetts program has enrolled half of the Commonwealth’s 600,000 uninsured citizens.

In the past, discussion of universal healthcare was frequently tied to the idea of a single payer, but today there is little serious consideration of moving toward such a payment system. None of the major presidential candidates favors a single-payer system, and there is little support for it in Congress. However, there is increasing discussion about requiring employers to provide coverage for their employees or contribute to some kind of coverage pool.

---

**How to prepare your plan for the future**

- Monitor for state and federal proposals that would require employers to provide insurance coverage to employees or contribute to an insurance pool, sometimes called a play-or-pay mandate.
- Stay abreast of congressional discussions about whether employer subsidies under Medicare Part D are producing the intended result of encouraging employers to maintain retiree healthcare benefits.

---

**MEDICARE INITIATIVES**

**Purchasing value. Raising quality.**

**Key insights**

- Medicare is leading the movement toward value purchasing, which could dramatically advance the quality of healthcare in the United States.
- New quality metrics will foster provider accountability and replace cost as the main competitive driver in the near future.

Over the past several years, Medicare has steadily introduced a growing number of incentives designed to improve quality in all settings where Medicare beneficiaries receive care. CMS has collaborated with a wide range of public agencies and private organizations to establish the metrics needed to ensure the success of these programs. These organizations have included the National Quality Forum (NQF), Joint Commission on Accreditation of Health Care Organizations (JCAHO), National Committee for Quality Assurance (NCQA), Agency for Health Care Research and Quality (AHRQ), and American Medical Association (AMA).

The following are a few examples of Medicare value-purchasing programs:

**Hospital quality initiative**

In this program, the payments hospitals receive for each discharge are tied to the results of a set of 10 quality measures. Hospitals that submit the required data receive the full update to their Medicare diagnosis-related group payments. Nearly all (98.3%) of the hospitals eligible to participate in this program are complying with the requirements of the provision.
Care management program
A 3-year pay-for-performance demonstration with physicians, this program is intended to promote the use of health information technology to improve the quality of care for chronically ill Medicare patients. Doctors who meet or exceed performance standards established by CMS for clinical delivery systems and patient outcomes will receive bonus payments for managing the care of eligible Medicare beneficiaries.

Quality incentives in Medicare Part D
CMS monitors many aspects of the care delivered to members enrolled in the Medicare Part D prescription drug program. In 2007, CMS began to assign star quality ratings to every organization participating in the drug program as a plan sponsor. These ratings are publicly available online at the Medicare Prescription Drug Plan Finder website and are intended to assist beneficiaries in selecting a plan. For 2008, CMS has announced that the star ratings will also be used to monitor performance improvement.

CMS awards stars on a 1-to-5 scale in three areas:
- Customer service
- Operations (filling prescriptions, handling eligibility information, etc.)
- Drug pricing information

Generally, a rating of at least three stars is considered acceptable. In awarding the ratings, CMS considers self-reported data from the plans, complaints from beneficiaries, and analysis of third-party reviewers.

In the future, Medicare star ratings may play an increasingly important role in a Medicare Part D plan’s ability to compete in the market. Much like the Medicare Advantage market of the 1990s, there will likely be a period of aggressive consolidation among Part D plan providers. Those who are able to expand into new markets vacated by other plans will have a chance to increase their market share of the Part D program. In determining whether to approve such an expansion, CMS may consider the plan’s star ratings in their current market. Plans with poor ratings may be required to improve service levels before they are allowed to compete in additional markets.

Medicare value-purchasing and monitoring initiatives may lead to a new era of accountability, in which providers will compete on quality more than cost. In such an environment, member satisfaction and medical error reduction will be the first priorities, and health-adjusted episodes of care will become the leading measurable unit for reimbursement. Providers can be expected to prosper or fail based on publicly available quality metrics, creating an increasingly compelling business case for improvements in the quality of care.

How to prepare your plan for the future
- Consider how you might incorporate elements of Medicare Part D’s value-purchasing initiatives into your pharmacy and medical benefit metrics.
- Work with your Medicare Part D prescription plan provider to understand CMS’s star rating and how you can work together to maintain or improve it.
BIOSIMILAR DRUGS

Slow progress. Great potential.

Key insights
- The United States lags behind Europe and Asia in developing a market for biosimilar drugs (follow-on biologics).
- Although pending legislation is encouraging, it is unlikely that a pathway for biosimilars will be established before 2010.

The passage of the Hatch-Waxman Act in 1984 expedited the availability of generic drug products, which have provided a safe and effective way to lower the cost of traditional medications. For years, many payers have hoped that a similar measure would help mitigate the growing costs associated with biologic medications.

Follow-on biologics are already available in some other parts of the world. In India, generics are available for several relatively simple biologics, such as human insulin and interferon (although this may be partially because of less rigorous legal protection of intellectual property). In 2004, the European Union took the lead among more regulated markets, establishing a legal framework for the production of “similar biological medicinal products.” The legislation requires the manufacturers of such products to demonstrate product quality and therapeutic equivalence with the originator brand through bioequivalence studies.

The creation of regulatory pathways for approving follow-on biologics in the United States has proven to be more difficult. With significant scientific and financial issues standing in the way, progress on the availability of follow-on biologics in this country is likely to be slow, at least for the immediate future.

Are biogenerics generics?
The most common term for follow-on biologics, biogenerics, is a misnomer compared with the way the term generics is used for traditional medications. The compounds in traditional drugs can be precisely replicated, so the active ingredients in traditional generic drugs are chemically identical to those in the equivalent brand-name drugs. Biologic medications, on the other hand, are compounds from biologic (i.e., living) matter and are generally made up of complex proteins. Although follow-on products could be manufactured that would be medically equivalent, they might not be precise copies of the branded medications. Since the products are not identical, the brand manufacturers could argue that the follow-on products should undergo the full set of clinical trials required of new medications. Companies that plan to develop follow-on biologics argue that the FDA should establish an approval process more closely related to the abbreviated new drug application (ANDA) process currently available to generic manufacturers. Through the ANDA process, a manufacturer needs to establish only that its compound acts similarly in human beings to the current brand-name product.

Legislative progress
Congresswoman Anna Eshoo recently introduced the Pathway for Biosimilars Act, which would amend the Public Services Health Act to permit the application for licensure of generic biologics. After a vigorous debate sparked by Senate legislation proposed by Senators Kennedy, Hatch, and Clinton (S1695), the Eshoo bill has been viewed as an attempt to find an acceptable compromise between the interests of the biotech and generic drug industries.

Under the Eshoo bill, an application for licensure of a follow-on biologic would have to demonstrate, among other things, that the product is biosimilar to a reference product, based on results of analytical studies, animal studies, and a clinical study. These results must be sufficient to demonstrate the safety and efficacy of the biosimilar product. Notably, the Department of Health and Human Services would have the right to waive analytical and animal studies. Such waivers would be informed by a guidance document for the product class in which the biosimilar product falls. This document, which
must be submitted in advance of any application, must include criteria for determining biosimilarity, interchangeability, and immunogenicity (if available).

The bill offers incentives for both generic and brand-drug manufacturers. The sponsor of the first biosimilar product determined to be interchangeable may receive a 24-month period of market exclusivity. The brand manufacturer may see its 12-year exclusivity after initial licensure increased to up to 14.5 years under certain conditions.

**Estimating the savings**

It is unrealistic to assume that follow-on biologics will generate the same kind of savings produced by traditional generics. In fact, several hurdles will have to be cleared before any savings can be realized:

- There is no pathway for the approval of follow-on biologics, and no legislation is likely to establish one until at least 2010.
- Facilities for manufacturing biologic medications can cost over $500 million, limiting both the number of generics that would be financially viable and the number of manufacturers willing to take the risk.
- By the time their patents expire, many biologic medications have already lost market share to newer and more effective products.
- Biologic medications vary greatly in the complexity of their proteins. The most complex would be exceptionally difficult to reproduce in a manner that achieves true bioequivalence. Initially, biosimilar products are most likely to be follow-on versions of relatively simple proteins, such as human insulin, beta-interferons, and human growth hormone.

**Untapped potential**

Although follow-on biologics are not likely to yield the same degree of savings as traditional generics, they may still dramatically reduce prescription costs. Given the substantial volume of biologics coming off patent over the next 7 years, even a relatively modest percentage savings could produce substantial reductions in cost. Biologics worth approximately $22 billion in current U.S. sales are scheduled to come off patent in this time period (Figure 4). This presents a large potential opportunity for savings when biosimilar versions of these products become available.

Figure 4. Market opportunity for biosimilar drug products

Source: Medco data; IMS (retail sales); manufacturers’ annual reports

Note: The figure shows the biosimilar market opportunity for biologics with expected patent expirations over the next 8 years. Market opportunity is based on 2007 U.S. retail sales. Expected patent expiration dates may change due to litigation, patent challenges, at-risk launches, and other factors.
How to prepare your plan for the future

- Consider modifying the summary plan description language in your plan to accommodate the eventual emergence of follow-on biologics. If the intent is to cover these relatively expensive products under different rules from those for inexpensive traditional generics, the plan language should make that clear.
- Lobby for legislation that creates a regulatory pathway for follow-on biologics by 2010.

BEHIND-THE-COUNTER MEDICATIONS

New hearings for a new class.

Key insight

- The FDA is seriously considering creating a new drug classification, behind-the-counter drugs, which would add to the existing classes of OTC and prescription drugs.

In November of 2007, the FDA heard arguments for the establishment of a new category of medications called behind-the-counter drugs. These drugs would be available to patients after counseling from a pharmacist and would not require a doctor’s prescription. The pharmacist would be required to perform a clinical evaluation of a patient before deciding to dispense a drug or to refer that patient to a physician.

Some precedent exists for this new medication category. Eleven countries, including the United Kingdom, have an established behind-the-counter drug class. In the United States, the relatively few medications dispensed behind the counter include emergency contraception (because of the need for age verification), pseudoephedrine (because it can be made into methamphetamine), and certain cough syrups that contain a small amount of codeine. The new class, if created, could greatly expand the number of medications available without a prescription. Medications being considered for behind-the-counter status include statins, migraine medications, nasal steroids, birth control pills, and erectile dysfunction medications.

Generally, the pharmacy community supports the creation of the new class, arguing that it would increase access to the medications in that class and lower the cost of healthcare. Some note that a behind-the-counter class is commonly used in many parts of the world. Most physicians oppose the measure, arguing that it raises important safety concerns and may reduce access to medications currently sold over the counter. It is unclear how much pharmacists would charge for clinical services under the new measure and what the impact would be on plan coverage as medicines are moved from either prescription or OTC status to behind-the-counter status. Although many clinical and regulatory issues remain to be resolved, an expanded number of medications will probably be available in a behind-the-counter class within 5 years.22

How to prepare your plan for the future

- Consider whether you will cover behind-the-counter drugs if the new drug class is implemented. Financial considerations may vary, depending on whether specific medications are reclassified from OTC or have migrated from prescription status.
Emerging trends in biologic sciences

“There is in biology at the moment a sense of barely contained expectations...of advancing into the unknown, and that where this advance will lead is both exciting and mysterious.”

—The Economist, June 14, 2007

PREDICTION

Over the next 5 years, pharmacogenomic testing will become an integral part of clinical practice for many commonly treated conditions.

This is an era of remarkable progress in the healthcare sciences. Advances in genomics—both in diagnostic tests and targeted medications—are providing prescribers with critical new information about which drugs will work for their patients. Researchers are on the threshold of creating vaccines that not only prevent a growing list of cancers but may cure them as well. RNA-based research is yielding new therapies that promise to be more potent and precise. A rapidly growing array of nanotechnology products is transforming the markets for medical devices, diagnostics, and pharmaceuticals. Of course, all such innovation comes at a price, and someone must pay the bills. Deciding what advances will be covered and under which benefit will become an increasingly complex problem.

PERSONALIZED MEDICINE

Advanced diagnostics. Greater precision.

Key insights

- Advances in genomic diagnostics are allowing physicians to make more precise prescribing and dosing decisions.
- Personalized medicine may provide tremendous benefits for plan sponsors, including improved patient adherence, increased medication efficacy, and enhanced patient safety.

Since no two people respond exactly the same way to the same drug, care would be improved if doctors had a way of predicting which drugs and what dosages would work best for individual patients. This is the essential promise of personalized medicine.

The future of personalized medicine is based on advances in the field of pharmacogenomics—an area of science that studies how a person’s genotype (genetic makeup) affects his or her response to medication. For a plan sponsor, pharmacogenomics provides a basis for better-informed coverage decisions and more cost-effective care for its members.

Reducing costs, improving care

Personalized medicine allows benefit managers to focus coverage on treatments that are safe and most likely to be effective for individual members. Personalized medicine is expected to reduce medical costs associated with adverse reactions to medications, as well as the substantial amount of money spent on medications that yield no therapeutic benefit. Figure 5 illustrates five drug categories for which the current approach of trial-and-error prescribing can lead to relatively poor response to medications. Of the $46.7 billion spent nationally on drugs in these categories, an estimated $17.5 billion, or 37%, is wasted due to poor therapeutic response.
The blood thinner warfarin provides a good example of the potential cost savings that can be realized with pharmacogenomic testing. The ability to more precisely determine a patient’s required dose could reduce the potential for serious bleeding episodes or a stroke. The Brookings Institution has quantified the potential clinical and financial advantages of integrating genetic testing into routine warfarin therapy. Brookings has concluded that Americans who use the drug could avoid 85,000 serious bleeding events and 17,000 strokes annually. The resulting healthcare savings would be an estimated $1.1 billion annually, with a range of about $100 million to $2 billion.25

Personalized medicine may also improve patient adherence to therapy. By minimizing side effects through improved efficacy, personalized medicine could overcome a significant barrier to adherence. Choosing medications on a personalized basis may lessen patient resistance to therapy and encourage the 31% of Americans who do not fill their initial prescription to start therapy.26 Personalized medicine may address adherence issues by instilling confidence that a given medication is likely to achieve the desired result.

Providing clinical evidence
Some physicians have argued that pharmacogenomic testing is theoretically sound but hasn’t been proven in clinical situations. Medco is working on closing the gap between theory and practice by collaborating with partners in designing, funding, and participating in two studies to assess the clinical value of pharmacogenomic testing.

- Medco is conducting a study with the Mayo Clinic to determine how diagnostic testing can help find the right dose more quickly for patients who use the blood thinner warfarin. The optimal dose of warfarin varies widely from patient to patient because of individual genetic factors. The goal of the study is to determine whether genetic testing can help reduce the risk of hemorrhage or stroke, the adverse outcomes associated with the overdosing and underdosing of warfarin. More than 2 million Americans currently take warfarin, so the results of the study are expected to have a far-reaching impact.

- In a second study, Medco is collaborating with LabCorp to evaluate the efficacy of tamoxifen in preventing breast cancer recurrence in patients who are poor metabolizers of the drug.

These studies are among the first to evaluate the benefits of personalized medicine in day-to-day clinical practice.

A growing number of new drugs are associated with diagnostic tests, and guidance on genetic testing is already provided in the labeling for several products. In 2007, Selzentry® (maraviroc) became the first drug to be approved in conjunction with an associated diagnostic test. The co-receptor tropism assay, called Trofile™, determines whether the drug will work against the specific HIV strain infecting the patient.
How to prepare your plan for the future

- Consider using the results of genetic or biomarker testing in determining appropriate coverage for certain high-cost or high-risk medications.
- Determine coverage policy for companion diagnostic tests used in clinical decision making.
- Evaluate exception policies for coverage of off-formulary drugs for patients with less common genotypes.

CANCER VACCINES

Preventing cancers today. Curing them tomorrow?

Key insights

- Cancer vaccines will radically change the way cancer is treated—and may even produce cures for certain cancers.
- Vaccines to help prevent cancer are already on the market.

Research into cancer vaccines has gained considerable momentum over the past several years. These vaccines are or will be used to prevent viral infections that can lead to cancer (prophylactic vaccines) or to treat existing cancers by boosting the immune response (therapeutic vaccines). Although only prophylactic vaccines have been approved by the FDA so far, nearly a dozen therapeutic vaccines are currently in Phase III clinical trials.

Prophylactic vaccines

Prophylactic cancer vaccines are intended to prevent viral infections that can lead to cancer. Two such vaccines are already available: The hepatitis B vaccine prevents infection with the hepatitis B virus, which can cause liver cancer, and Gardasil® prevents infection with viruses associated with 70% of cervical cancer cases worldwide. An additional vaccine related to cervical cancer, Cervarix®, is under investigation.²⁷

Therapeutic vaccines

Therapeutic vaccines can be broadly separated into two categories: patient-specific vaccines that use a patient’s own cells to generate a vaccine which targets his or her specific cancer, and more general vaccines that target larger populations of cancer patients. In both cases, the vaccines take advantage of the fact that certain molecules are found only in cancer cells or are found there in greater abundance. These molecules, either carbohydrates or proteins, act as antigens. That means they have the potential to stimulate an immune response, mounting an attack on the cancer cells while leaving the noncancerous ones alone.

Many of these vaccines treat only specific kinds of cancers, because certain antigens are unique to those cancers. Among the cancers targeted by therapeutic vaccines currently in Phase III trials are non-Hodgkin’s lymphoma, kidney cancer, cutaneous melanoma, ocular melanoma, prostate cancer, and multiple myeloma.

The first therapeutic vaccine

Provenge® (sipuleucel-T) is a cancer vaccine developed by Dendreon Corp. This vaccine shows promise in the treatment of metastatic prostate cancer that is unresponsive to hormone therapy. If approved, Provenge would provide another treatment for men who currently have few options. The Provenge vaccine is made by combining a patient’s own cells with a protein that revs up the immune system and causes it to attack the tumor. The vaccine would be the first one designed to treat existing cancer, rather than to prevent the disease from occurring.
In a clinical trial of 127 men, Provenge helped vaccinated men live about 4.5 months longer than those given placebo. However, there was no difference in how long it took for the men’s cancers to begin growing again. Dendreon is conducting a Phase III trial to test Provenge in men whose metastatic prostate cancer worsened while they were on hormone therapy. In March 2007, an FDA advisory committee reported that there was substantial evidence for the safety and efficacy of the vaccine. In May 2007, the FDA announced that more data would be necessary for drug approval.

How to prepare your plan for the future

- Consider covering prophylactic vaccines and selected therapeutic vaccines under the pharmacy benefit. Patient-specific therapeutic vaccines are best covered under the medical benefit, but cancer vaccines targeted at broader populations could be covered under the pharmacy benefit.

### CASE STUDY: COVERING VACCINATIONS THROUGH THE PHARMACY BENEFIT

To boost productivity, a state government employer sought to increase flu immunization rates among its employees. The employer implemented an innovative program to provide flu vaccines—at no cost to plan members—through a statewide network of retail pharmacies.

When employees become sick with influenza or are absent to care for sick family members, the employer incurs costs in lost productivity. As part of its routine wellness benefit, the government plan pays 100% for flu shots given at physicians’ offices. However, many employees and covered family members were not taking advantage of this benefit. The plan sought an innovative solution that would expand access to the shots and boost immunization rates.

**Actions**

In the state where the government plan operates, licensed pharmacists are allowed to administer flu shots. Medco worked with the plan to establish a special statewide preferred provider network of pharmacies to provide flu shots to plan members. Employees and their dependents could simply present their card at a network pharmacy, receive a flu shot, and have it covered at no charge under their prescription benefit. The benefit plan reimbursed the pharmacies at a rate of $25 per vaccination.

**Outcomes**

As awareness of the flu shot program expanded, the number of plan members who received flu shots increased rapidly.

- During the 2006–2007 flu season, the first year of implementation, almost 15,000 flu shots were provided through local participating pharmacies.
- The number of flu shots administered under the medical benefit also grew nearly 16%, from about 16,800 in 2006 to more than 19,400 in 2007.
- Nearly 14,000 flu shots have already been provided under the pharmacy benefit during the 2007–2008 flu season.

The plan sponsor has decided to extend the program for the 2008–2009 season and may expand the scope to include other vaccines. The program has become a model adopted by other states to reduce absenteeism and improve employee productivity.
RNA INTERFERENCE

Targeting the messenger

Key insights
- Drug development based on RNA interference (RNAi) is a relatively new and highly promising field of research.
- RNAi may be harnessed to selectively “turn off” specific genes, producing highly targeted drug therapies.

If DNA is the blueprint for building cells and proteins are the primary building blocks, then RNA is the construction foreman. Certain forms of RNA act as messengers that instruct cells regarding which proteins must be produced to carry out cellular activities.29 The relatively recent realization that RNA performs a wide range of structural and functional activities beyond simply carrying genetic information has spurred research directed at using RNA targets to create new therapeutics.30

Scientists have long understood RNA’s role in building proteins. First, DNA is copied onto a corresponding piece of single-stranded messenger RNA (mRNA), which delivers the information to the cell’s protein-synthesis machinery. Beyond acting as a simple passive messenger, RNA also plays a role in building proteins. The ribosome, which makes proteins, is made partly of RNA, and transfer RNA (tRNA) aids in protein production.31

Running interference
Most traditional drug research focuses on protein function. The mapping of the human genome has also allowed scientists to use gene therapies to target DNA. RNA represents a third front, targeting the intermediary between DNA and the end point of protein synthesis.

One of the more promising areas of research focuses on a naturally occurring process called RNAi. This process, which scientists believe evolved from an early defense against viruses, is essentially a mechanism to shut down specific genes. Short, unique pieces of double-stranded messenger RNA (RNA is usually single stranded) are called small interfering RNA (siRNA) molecules. Specific siRNA molecules target specific mRNA molecules, thereby blocking production of the proteins that are end-products of the gene-activation process.

Designing new drugs
In drug development, researchers employ RNAi as a mechanism to shut off unwanted genetic activity in a targeted manner. Scientists copy double-stranded RNA (dsRNA) from the gene they wish to shut off and introduce it into the cell. The dsRNA finds and degrades the matching mRNA, effectively stopping the activity of the targeted gene and the subsequent production of its proteins.31

RNAi research may yield a variety of novel drug therapies. Theoretically, techniques could be developed to turn off genes that produce cancer or to combat chronic viruses such as those that cause hepatitis and AIDS. More than 20 companies are currently researching commercial applications of RNAi techniques. Therapeutic products in development include Alnylam’s ALN-RSV01, a therapy for respiratory syncytial virus that is currently in Phase II human trials,32 and Opko’s bevasiranib, a therapy for wet age-related macular degeneration and diabetic macular edema that is currently in Phase III clinical trials.33 A steady stream of new products can be expected to enter clinical trials as a result of the highly promising RNA-based avenues of research.34
How to prepare your plan for the future
- Monitor the pipeline for the first commercial RNAi-based drug therapies and plan how to position these novel products in your current pharmacy and medical benefit structure.

NANOMEDICINE
Small scale. Big market.

Key insights
- The total market for nanomedicine products is expected to surpass $100 billion by 2020.
- Nanotechnology will provide revolutionary ways of designing new drugs and diagnostics.

Nanotechnology exploits the unique physical, chemical, and biologic properties of materials at the molecular level, enabling improved devices, systems, and materials to be developed. Already, nanotech applications have appeared in many industries, including cosmetics, sports equipment, and textiles. In the healthcare industry, nanotechnology is beginning to transform medical practice with new drug delivery methods, diagnostics, therapeutics, and pharmaceuticals.

For perspective, the diameter of DNA, our genetic material, is in the 2.5-nanometer range, whereas the diameter of red blood cells is approximately 2.5 micrometers (about 1,000 times larger). By intervening at the nano level, where biologic structures and molecules inside the living cell operate, researchers hope to diagnose and cure disease, as well as repair damaged skin, bone, and nerve tissue. According to a study by the Freedonia Group, a market research firm, gains will come through the introduction of new, improved cancer and central nervous system therapies.

Although still in its infancy, the nanomedicine market is growing rapidly. Demand for nanotech healthcare products in the United States is projected to grow by nearly 50% annually to approximately $6.5 billion in 2009. The total nanomedicine market will exceed $100 billion by 2020, as substantial technical and regulatory barriers—such as determining whether some of the products should be regulated as drugs or devices—are overcome.

How to prepare your plan for the future
- Review medical and pharmacy coverage policies as new nanotechnology-based medications, devices, and diagnostics come to market.
One sure-fire prediction

More than 40 years ago, the implementation of Medicare transformed the healthcare landscape. Current advances in information technology and the biologic sciences—coupled with policy changes and the rise of consumerism—will have an even more dramatic effect on the future course of healthcare. New technologies, drugs, and diagnostic tests will greatly expand the ability to prevent and treat disease. However, some of these innovations will add complexity to the system, and none of them will be free. The nation’s ability to provide access to care will be commensurate with its ability to lead, understand, and adapt to these changes.
REFERENCES

FOCUSING ON TREND | A LOOK BACK AT 2007


PROJECTING THE FUTURE  |  A LOOK AT THE NEXT THREE YEARS


**SCANNING THE HORIZON | FIVE INSIGHTS THAT WILL SHAPE HEALTHCARE**


WE WOULD LIKE TO ACKNOWLEDGE THE FOLLOWING PEOPLE FOR THEIR OUTSTANDING CONTRIBUTIONS TO THE 2008 DRUG TRENDS REPORT:

Robert S. Epstein, M.D., M.S.
Jack A. Smith, M.A.
Lynn Costello, M.D.
Bob B. Verheugge, Ph.D.
Brad Epilese
Glen Hendling, M.S.
Roy Anthony
Libby Meil
Keith Bradbury, R.Ph., M.S.
Peter van Dijk
Kevin Cinsky Pharm.D., M.B.A.
Bill Drellian, Pharm.D.
Mark Boyer
Valerie Traum
Michael Eliafonte

Publisher, Chief Medical Officer
Publisher, Chief Marketing Officer
Editor in Chief
Managing Editor, Senior Writer
Executive Creative Director
Creative Director
Brand Steward
Project Manager
Senior Writer
Senior Writer
Contributing Writer
Contributing Writer
Senior Editor
Contributing Editor
Senior Production Manager

Analytic support
Kai C. Chan
Al DeCarlo
Susan Ganasgaga, Ph.D., M.B.A.
Rose Healey
Tony Joseph
Thomas Kanterhouse, M.S., M.B.A.
Mona Khalid, M.B.A.
Kamil Patel
Miriam Rykin, M.S.
Jodi Schreiber
Hannah Suy, R.Ph., M.B.A.
Richard Thornton

Additional contributors
Peter Beggs
Indeep Bhandar, Ph.D.
Carolee Castellanos, M.A.
Andrew Chua
Patricia Dodds
Woody Eisenberg, M.D.
Darnell Fatigati
Susan Faust
David Fulcher
Tracy Grunfeld
Bill Heat, J.D.
Scott Hemus
Jennifer Luddy
Ken Mallory, M.B.A.
Colleen Manley
Joe Marsalito
Barbara S. Mersen, M.P.H.
Michael Pollard, J.D., M.P.H.
Steve Russell, R.Ph.
Alexander Shinkarz, J.D., M.H.S.
Ann M. Smith, M.S.
Scott Stratton, M.P.H.
Anna Wong, M.P.H.

Account team contributors
Judy H. Allen, Pharm.D.
Francine Bellafatto, R.Ph., M.B.A.
Kim Brown
Jennifer Conroy
Karen DeZunzum, Pharm.D.
Patsy Felicita, M.B.A.
Carlyon Guglielmone
Matthew Pelleia, M.B.A.
Alison Robertson
Marie Sargent, R.Ph.
Jeff Scott

Contributing writers
Begins
Bhandar
Castellanos
Chua
Dodds
Eisenberg
Fatigati
Faust
Fulcher
Grunfeld
Heat
Hemus
Luddy
Mallory
Manley
Marsalito
Mersen
Pollard
Russell
Shinkarz
Smith
Stratton
Wong

Contributing editors
Hemus
Luddy

Production manager
Luddy

All rights in the product names, trade names, or logos of all third-party products appearing in rabios in this report, whether or not appearing with a trademark symbol, belong exclusively to their respective owners.

Medco, medco, Preferred Prescriptions, RationalMed, and Medco Therapeutic Research Center are registered trademarks of Medco Health Solutions, Inc. All the Heart of Health and RationalMed are trademarks of Medco Health Solutions, Inc.

© 2008 Medco Health Solutions, Inc. All rights reserved.

Designed and produced by regards.com.
PREDICTIONS
Five insights that will shape healthcare