2006 Vol 8

DRUGTREND REPORT

Personalizing Healthcare

The Promise, The Cost, The Solution

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To our clients and friends:

We are pleased to report that by working together, we were able to reduce drug trend in 2005 to 5.4%—its lowest level in many years. The primary reasons for the slower growth are cost savings associated with the increased use of generics and more careful utilization management. However, significant challenges remain—including a growing number of new prescription medications and the rapidly increasing costs of providing specialty care.

In our 2006 *Drug Trend Report*, we analyze the factors driving prescription drug spending and use projections to look ahead through 2008. The report offers strategies for reducing trend, such as taking advantage of the upcoming billion-dollar generics savings opportunity. Also, we have added a new data section that compares plan sponsors' benefit offerings against those of their peers. This section provides practical tips for managing prescription drug benefits, and case studies that illustrate benefit management approaches that have achieved impressive results.

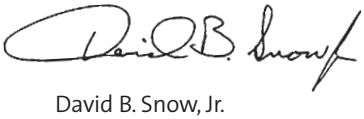
Personalized strategies for a new era of healthcare

Some intriguing developments in personalized healthcare are also on the horizon. Medications that are targeted to individual patients will shift prescribing to an "identify and treat" model instead of the traditional "treat and adjust" approach. This shift will present exciting new opportunities for prescription care, as well as significant challenges for managing the pharmacy benefit. To help plans prepare for these challenges, this year's report focuses on the emerging field of pharmacogenomics.

New ways of thinking about management strategies will be the key to staying ahead of these changes in the healthcare environment. Plans will need to continually reassess their benefit designs in light of healthcare trends and their overall benefit philosophy. Here, we introduce the concept of **PBM DNA**™—the characteristics that define how and why plans make certain benefit management choices.

We hope you will find this information valuable as you define your evolving role in this new arena of personalizing healthcare.

Sincerely,



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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**.

DRUG TREND REPORT ▪ 2006
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5-31 2005 IN REVIEW **THE FINGERPRINT OF TREND** ■

For Medco clients, drug trend averaged 5.4%—its lowest level in many years. Careful management of prescription benefit plans has helped rein in drug costs for the nation as a whole.

Utilization grew at a relatively slow pace in 2005. Treatment rates increased rapidly for many long-term medications, but the use of nonnarcotic pain relievers declined sharply due to continuing concerns about their cardiovascular safety. Utilization growth was especially strong for sedative-hypnotics.

Unit costs grew slowly, in spite of explosive growth in the use of high-cost biologics. The inflationary pressure from brand-name drugs was offset by a significant increase in the use of low-cost generics.

Spending growth in 2005 was concentrated in a few therapeutic classes, including medications used to treat high cholesterol, rheumatoid arthritis, asthma, diabetes, and cancer. Growth was especially strong for specialty drugs, which have emerged as the largest single driver of drug trend. Spending for specialty drugs increased 16.9%.

Patterns of medication use vary widely by state, gender, age, and disease burden. Patients with chronic and complex conditions have the highest rates of utilization, and they offer the greatest opportunity for cost management through personalized healthcare.

2005 IN REVIEW:
THE FINGERPRINT OF TREND

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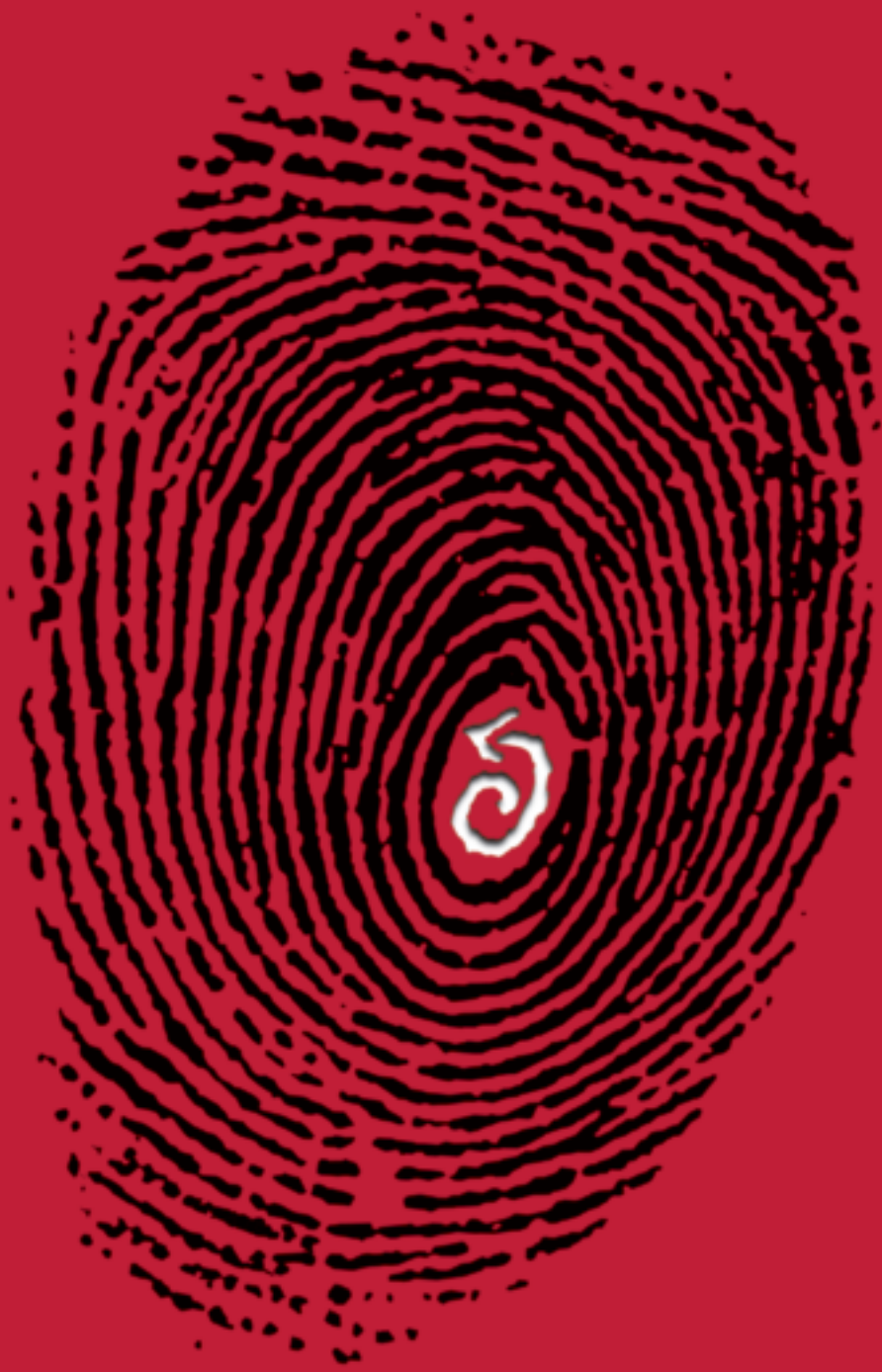


The imprint of the past is the starting point for change.

This section will help you:

- **Understand the forces that helped keep drug trend low in 2005.** Unit costs grew slowly, as the use of generic drugs increased in many therapeutic areas. A sharp decline in the use of COX-2 inhibitors helped offset the rapid increase in treatment rates for many chronic conditions.

- **Identify emerging growth areas that may require proactive management.** Specialty drugs are the fastest growing segment of pharmacy costs. Utilization is also growing rapidly for many medications used on a long-term basis. Areas of rapid spending growth include cancer drugs and sedative-hypnotics.

Trend in profile

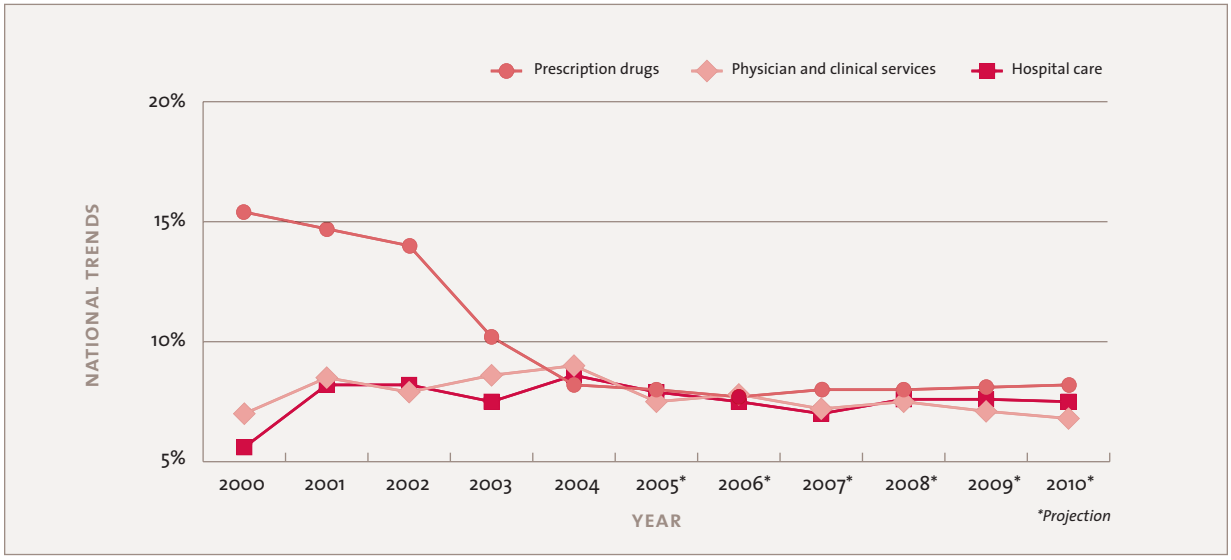
Through careful management of utilization and cost, Medco clients have reduced drug trend to its lowest level in many years. The average cost of prescription drug benefits rose only 5.4% in 2005—well below the 8.5% increase in 2004.* Growth rates have declined substantially from the double-digit rates of preceding years.

The number of clients achieving single-digit trend has been increasing rapidly. In 2005, 79% of Medco's top integrated accounts achieved trend below 10%, compared with 54% who achieved single-digit trend in 2004. In 2005, half of Medco's integrated accounts achieved trend below 4.9%.

*Reported trends are based on 2 years' data on pharmaceutical spending, representing 86% of the $38 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 and member cost share have been applied. Drug trend is the percent change in plan spending from one year to the next.

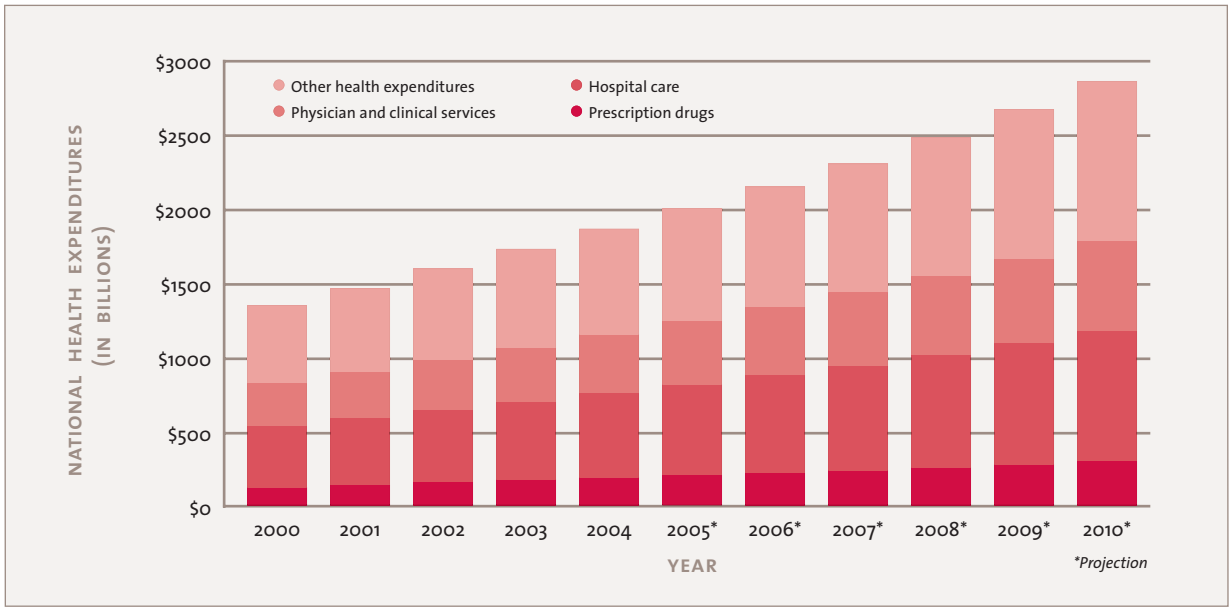
The declining trend for private-sector prescription plans has had a significant impact on national healthcare costs. For many years, retail drug spending has been the fastest growing component of national healthcare expenditures (Figure 1), but in 2004 it was outpaced by spending for hospital care and physician services.[1,2] The slowdown in prescription drug spending was a major contributor to the overall slowdown in national healthcare costs in 2004.[2]

Figure 1. National healthcare cost trends from 2000 to 2010
Source: Centers for Medicare and Medicaid Services[1]



According to projections by the Centers for Medicare and Medicaid Services, drug trend is likely to remain moderate over the next few years (Figure 1), and retail drug spending will continue to represent 10% to 11% of total national healthcare costs (Figure 2).[1]

Figure 2. National health expenditures from 2000 to 2010
Source: Centers for Medicare and Medicaid Services[1]

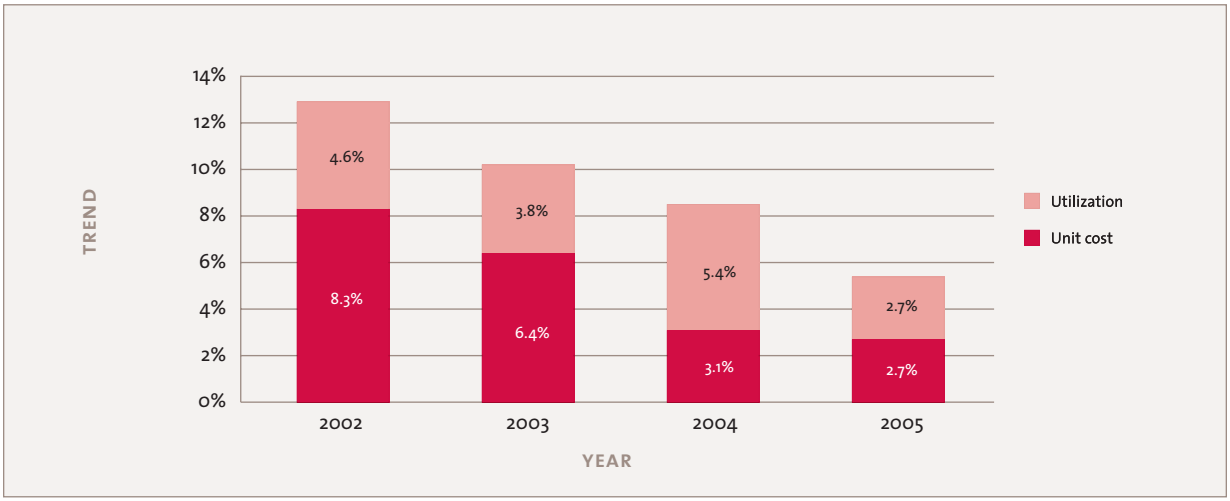


Note: "Other health expenditures" include nursing home care, home healthcare, dental services, medical equipment, government expense, and investment costs.

KEY GROWTH DRIVERS

The primary contributors to drug trend are utilization and unit cost. In 2005, these factors contributed equally to the overall growth in drug spending for Medco clients. Across all therapeutic categories, utilization grew an average of 2.7%, and unit costs rose 2.7% (Figure 3).

Figure 3. Changes in trend drivers over the past 4 years
Source: Medco data



Note: The figure shows the contributions of utilization growth and unit-cost growth to total trend. Trend is the percent change in plan spending compared with the prior year.

- **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*.

  The utilization growth in 2005 was largely due to a rapid increase in the number of members receiving medication treatment for chronic conditions. This growth was offset by utilization declines in a few therapeutic categories.

- **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 plan cost per day of therapy.

  In 2005, unit-cost growth was primarily driven by price increases for single-source brand-name drugs. These inflationary pressures were offset by a significant increase in the use of generic drugs.

Over the past 5 years, the relative impacts of these two trend components have varied widely, but the net effect has been a progressive reduction in overall trend (Figure 3). Since 2002, unit-cost growth has shown a consistent and remarkable pattern of decline—from 8.3% in 2002 to 2.7% in 2005. The increased availability and use of generic drugs has been a major contributor to this decline in cost inflation, and it has been a major contributor to the decline in overall trend.

Utilization growth has shown a more variable course year-to-year, but the general trend has been downward (falling from 8.2% in 2001 to 2.7% in 2005). The overall trend demonstrates the sustained impact of plan management initiatives, but utilization has also been affected by market changes that are more variable and less predictable. For example, the over-the-counter conversion of *Claritin*® products in late 2002 had a large one-time impact on utilization growth in 2003, and safety concerns regarding COX-2 inhibitors had a large impact on utilization growth in 2005.

Utilization: Trends in treatment

Utilization grew at a slower pace in 2005 than in 2004, but there were wide variations by therapeutic class. For many medical conditions, treatment rates increased rapidly in 2005.

MORE PATIENTS, MORE MEDICATIONS

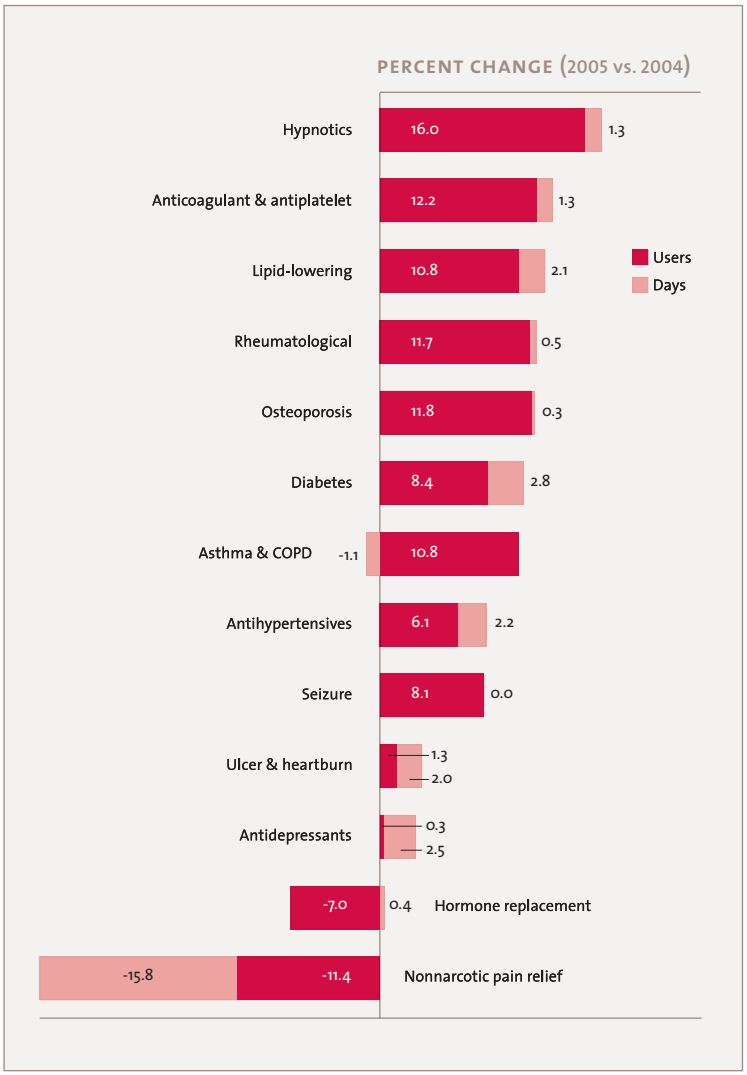
About 72% of plan members filled at least one prescription during 2005—a slight increase over the rate in 2004. However, the average number of treatment days per user increased almost 4%. Some of this growth was due to an increase in *treatment rates* (the number of users receiving treatment for a condition), and some was due to an increase in *treatment intensity* (the number of treatment days per year). Figure 4 shows the changes in treatment rates and intensity for therapies that are frequently prescribed on a long-term or chronic basis.

For most long-term therapies, utilization growth was primarily driven by an increase in treatment rates, while changes in treatment intensity were generally more moderate. Treatment rates increased dramatically—more than 10%—for sedative/hypnotic, antiplatelet, osteoporosis, rheumatological, respiratory, and lipid-lowering medications. Treatment rates declined sharply for nonnarcotic pain relievers and hormone replacement therapies.

Among the therapies showing high utilization growth, treatment intensity grew most strongly for lipid-lowering, diabetes, and antihypertensive medications. The increased number of therapy days may reflect improved medication adherence, but it may also reflect an increase in the use of multiple-drug therapies for these conditions.

For nonnarcotic pain relievers, the large decrease in utilization reflects declines in users and days in almost equal measure (Figure 4). Although some users of COX-2 inhibitors have shifted to traditional nonsteroidal anti-inflammatory drugs (NSAIDs), many stopped using nonnarcotic analgesics altogether—leading to a sharp decline in treatment rates for this therapeutic class. Safety concerns surrounding all of the medications in this class, including the traditional NSAIDs, may have contributed to the large decline in average days of use for people who continued to use these medications.

Figure 4. Changes in utilization for selected therapeutic classes in 2005
Source: Medco data



Note: The figure shows the contribution of treatment rate (users) and treatment intensity (days) to utilization growth in 2005. Data are shown for therapies that are frequently prescribed on a long-term or chronic basis. Users are measured on a per-member basis, and therapy days are measured per user per year. The X axis shows the percent change in each measure compared with the prior year. Therapeutic classes are rank-ordered from the largest utilization growth (at the top) to the largest utilization decline (at the bottom).

The utilization growth rates for individual therapeutic classes look different from the overall pattern of growth, and the difference creates a paradox. If treatment rates are rising so quickly for so many medical conditions, how can the overall number of medication users be rising so slowly? The answer to the paradox is that many medication users are taking multiple drugs. In general, patients who start new treatments also take other medications during the course of the year. Utilization growth is primarily driven by users of multiple medications.

■ DYNAMICS OF UTILIZATION GROWTH

Given the wide variations across therapeutic classes, it is unlikely that any single factor accounts for the overall pattern of growth in 2005. Each therapeutic area is affected by a unique mix of clinical, regulatory, and market forces. The primary forces at play in 2005 included:

New drugs

The pace of new drug approvals has been relatively slow over the past few years.[3] In 2005, only 18 new molecular entities and two therapeutic biologics were approved by the FDA (Table 1). The first-year impact of these drugs on utilization was relatively small, since many were introduced late in the year and some are indicated for low-prevalence conditions. However, several of the new drugs approved in 2004 had a significant impact on utilization growth in 2005, their first full year of market availability. Some of these drugs are indicated for higher-prevalence conditions and showed rapid share growth in 2005. Examples are *Lunesta*™ (insomnia), *Spiriva*® (chronic obstructive pulmonary disease), and *Cymbalta*® (depression, diabetic peripheral neuropathy).

Table 1. New drug introductions in 2005
Source: *The Pink Sheet*[4]

Quarter	Brand name	Generic name	Use
1Q 2005	*Symlin*®	pramlintide	Type 1 or 2 diabetes
	Baraclude®	entecavir	Chronic hepatitis B
	Mycamine®	micafungin	Fungal infections
2Q 2005	*Byetta*®	exenatide	Type 2 diabetes
	Levemir®	insulin detemir	Type 1 or 2 diabetes
	Aptivus®	tipranavir	HIV
	Tygacil®	tigecycline	Bacterial infections
	Naglazyme™	galsulfase	Mucopolysaccharidosis VI (MPS VI)
3Q 2005	***Increlex***™	mecasermin	Growth failure
	Rozerem™	ramelteon	Insomnia
	Nevanac™	nepafenac ophthalmic suspension	Ophthalmic pain and inflammation
4Q 2005	***Revlimid***®	lenalidomide	Myelodysplastic syndromes
	Orencia®	abatacept	Rheumatoid arthritis
	Nexavar®	sorafenib	Renal cell carcinoma
	iPlex™	mecasermin	Growth failure
	Exjade®	deferasirox	Chronic iron overload
	Vaprisol®	conivaptan	Euvolemic hyponatremia
	Arranon®	nelarabine	Leukemia, lymphoma
	Hydase™	hyaluronidase	Dispersing agent for injectables, hypodermoclysis
	Hylenex™	hyaluronidase	Dispersing agent for injectables, hypodermoclysis

Note: The table shows the new molecular entities and therapeutic biologics approved by the FDA during 2005.
Bold text indicates specialty drugs.

New indications

As the drug pipeline for new medications has slowed, manufacturers have focused increasingly on new indications for current products as a means of expanding their markets. Although there may have been some prior off-label use of a product for the new indication, FDA approval permits manufacturers to advertise the new indication to physicians and consumers. Some of the principal new indications approved during 2005 are shown in Table 2. Many of these drugs were significant drivers of utilization growth within their therapeutic classes.

Changes in clinical practice

In several therapeutic areas, heightened attention to safety risks has led clinicians to be more cautious in prescribing certain types of medications, leading to slower utilization growth or an overall decline in use.

- **Antidepressants.** Utilization growth for antidepressants has slowed considerably over the past few years, responding to growing concerns about the possible risk of increased suicidality in both children and adults, especially during the first few months of therapy or when dosages are adjusted.[6,7]
- **Nonnarcotic pain relievers.** Concerns over the potential cardiovascular risks of COX-2 inhibitors have led to a sharp reduction in the use of nonnarcotic analgesics.[8,9] This decline was a major contributor to the overall slowing of utilization growth during 2005; it lowered the overall growth rate by 24%. The market withdrawal of two COX-2 inhibitors, *Vioxx*® (September 2004) and *Bextra*® (April 2005), contributed to the decline. Although some users of these products shifted to traditional NSAIDs or to *Celebrex*®, many discontinued use of prescription products in this class.
- **Hormone replacement.** Safety and efficacy concerns have led to a continuous, multiple-year decline in the use of hormone replacement therapy, based on the results of the Women's Health Initiative and other studies.[10-13] Use of these therapies continued to decline in 2005.

In each of these therapeutic areas, clinical assessments of the balance between risk and benefit have changed over time, leading to significant changes in prescribing patterns.

Disease prevalence

Increased prevalence and improved diagnosis have probably contributed to utilization growth in some therapeutic classes. The epidemic of obesity in the United States has accelerated the prevalence and treatment of diabetes,[14,15] which is reflected in the steady utilization growth for diabetes medications. For age-related conditions, such as osteoporosis and hypertension, prevalence is likely to increase as the demographic distribution shifts to older age groups. For other conditions, such as asthma and diabetes, prevalence has been increasing across a broad range of age groups for more than 20 years.[14,16] In all of these areas, treatment rates increased rapidly in 2005 (Figure 4).

Utilization management

During 2005, many of Medco's clients expanded their use of plan management tools that can help moderate utilization growth. These tools include tiered formulary and co-payment designs, prior authorization, dispensing quantity limits, and other techniques for managing utilization when it is clinically appropriate. Some of the potential benefits of these tools are discussed later in this report, beginning on page 70.

Table 2. Approvals for new indications in 2005
Source: U.S. Food and Drug Administration[5]

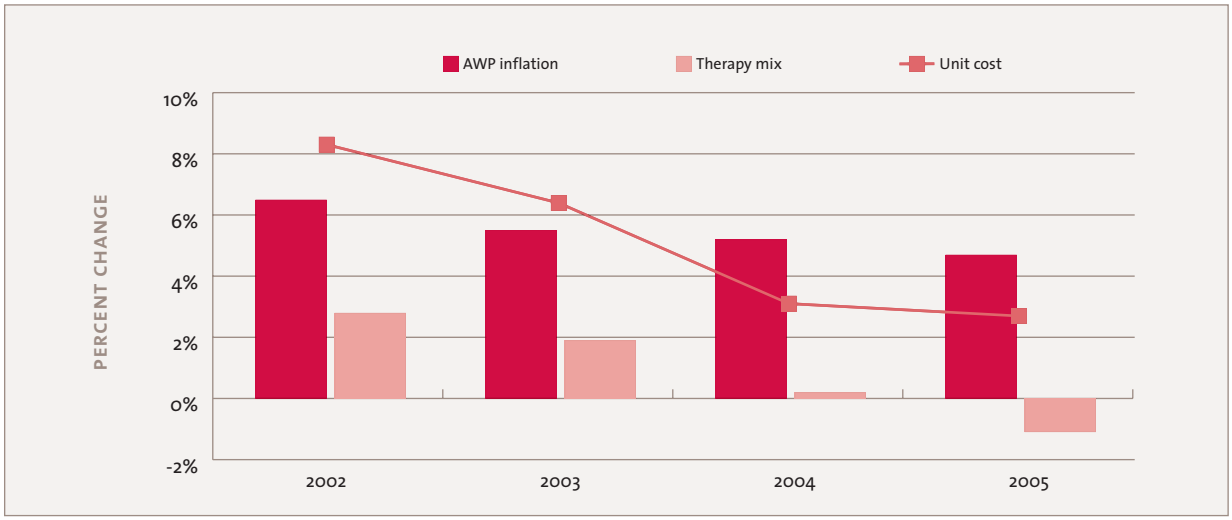
Quarter	Brand name	Generic name	Brief description of new use*
1Q 2005	*Abilify®*	aripiprazole	Maintenance therapy in bipolar I disorder
	Boniva®	ibandronate	Once-monthly treatment of postmenopausal osteoporosis
	Avandia®	rosiglitazone	Use in combination with a sulfonylurea and metformin (triple therapy)
2Q 2005	*Requip®*	ropinirole	Restless legs syndrome
	Atacand®	candesartan	Treatment of heart failure (NYHA class II-IV) in patients with left ventricular systolic dysfunction (ejection fraction <40%) to reduce cardiovascular death and to reduce heart failure hospitalizations
	Lyrica®	pregabalin	Adjunctive therapy for adult patients with partial onset seizures
	Nutropin®	somatropin	Long-term treatment of idiopathic short stature
	Arixtra®	fondaparinux	Use in patients undergoing abdominal surgery
	Remicade®	infliximab	Treatment of psoriatic arthritis
	Pegasys®	peginterferon alfa-2a	Treatment of chronic hepatitis B
3Q 2005	*Singulair®*	montelukast	Perennial allergic rhinitis in adults and children 6 months of age and older
	Celebrex®	celecoxib	Relief of signs and symptoms of ankylosing spondylitis
	Diovan®	valsartan	Use after myocardial infarction to reduce cardiovascular mortality in stable patients with left ventricular failure or dysfunction
	Mobic®	meloxicam	Relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years of age and older
	Aceon®	perindopril	Use in stable coronary artery disease to reduce the risk of cardiovascular mortality or nonfatal myocardial infarction
	Lipitor®	atorvastatin	Use in adults with type 2 diabetes and without clinically evident coronary heart disease, to reduce the risk of myocardial infarction and stroke
	Remicade®	infliximab	Second-line treatment of moderate-to-severe active ulcerative colitis
4Q 2005	*Depakote® ER*	divalproex extended-release tablets	Acute manic or mixed episodes associated with bipolar I disorder, with or without psychotic features
	Femara®	letrozole	Adjuvant treatment of postmenopausal women with hormone-receptor–positive early breast cancer
	Tamiflu®	oseltamivir	Prophylaxis of influenza in children 1 to 12 years of age
	Aromasin®	exemestane	Adjuvant treatment of postmenopausal women with estrogen-receptor–positive early breast cancer who have received 2 to 3 years of tamoxifen, to complete 5 consecutive years of adjuvant hormonal therapy
	Humira®	adalimumab	First-line therapy in moderate-to-severe rheumatoid arthritis
	Avelox®	moxifloxacin	Treatment of complicated intra-abdominal infections
	Tarceva®	erlotinib	In combination with gemcitabine for the first-line treatment of advanced pancreatic cancer
	Effexor® XR	venlafaxine extended-release capsules	Long-term and short-term panic disorder
	Xyrem®	sodium oxybate	Excessive daytime sleepiness in patients with narcolepsy
	Levemir®	insulin detemir	Pediatric patients with type 1 diabetes

Note: The table shows some of the efficacy supplements (new or expanded uses) approved by the FDA during 2005.
Bold text indicates specialty drugs.
*Check product label for the exact wording of the new indication.

Unit costs: The power of generics

Unit costs grew at a slower pace in 2005 than in 2004. This continues a progressive decline in unit-cost growth that began in 2002 (Figure 5). The primary force behind this decline is the increased use of generic drugs.

Figure 5. Changes in unit cost over the past 4 years
Source: Medco data



Note: The figure shows the contributions of AWP inflation and therapy mix to unit-cost growth. Unit-cost growth is the net effect of changes in manufacturer prices, therapy mix, member cost share, discounts, and rebates. The Y axis shows the percent change compared with the prior year.

DYNAMICS OF UNIT-COST GROWTH

The primary contributor to unit-cost growth in 2005 was a 4.7% average increase in manufacturer pricing for the drugs used by plan members (Figure 5). This inflationary force was offset by other pricing factors that reduced the net inflation rate to only 2.7%. The primary offsetting factor was the continuing shift in therapy mix toward generic medications (–1.1%).

Price inflation

Average wholesale price (AWP) inflation continues to exceed the rate of inflation in the U.S. economy as a whole.[1] Price inflation has been especially strong for brand-name drugs, many of which are protected by patent from market competition. Prices increased 6.3% for brand-name drugs during 2005, but they rose only 0.3% for generic drugs, which generally face pressure from competitive products. The overall price inflation in 2005 (4.7%) reflects the mix of brand and generic drugs used by plan members.

For Medco clients, AWP-based price inflation has declined progressively over the past 4 years (Figure 5). Part of this decline can be attributed to the slower price inflation for brand-name drugs, which dropped from 6.7% in 2004 to 6.3% in 2005. However, the decline also reflects the gradual shift toward increased use of generic drugs. As more prescriptions are dispensed using generics, aggregate price inflation will tend to decline because of the lower inflation rate for generic products. The average generic dispensing rate for Medco clients increased from 46.3% in 2004 to 51.5% in 2005. This was a key factor in the decline in price inflation over the same period.

Therapy mix

Unit-cost changes varied widely by therapeutic class during 2005, depending on the mix of brand-name and generic products. Large increases in unit cost were found for some therapeutic classes where few or no generic alternatives are available. In these cases, costs were driven upward by price increases on brand-name drugs or by shifts in product mix toward higher-cost brands. Examples include rheumatological drugs, cancer drugs, and insulin products. Large reductions in unit cost were found for some therapeutic classes where all or most of the therapeutic options are available in generic form. In these cases, price competition among manufacturers has reduced unit costs. Examples include thyroid medications and angiotensin-converting enzyme (ACE) inhibitors.

Managing price inflation

The impact of AWP inflation was moderated by discounting and cost sharing in 2005. Discounting helped reduce unit-cost growth to only 2.7%—well below the 4.7% increase in manufacturer prices. Changes in cost sharing had little net effect on unit-cost growth in 2005.

Discounting. Through its retail network and its mail-order pharmacy service, Medco provides its clients with substantial discounts off average wholesale prices. Medco secures additional discounts by negotiating rebates from many drug manufacturers for products that are on plan formularies. Using these discounts, Medco and its clients can substantially reduce the net cost of prescription drugs purchased under pharmacy benefit plans.[17,18] Plans can maximize their use of lower-net-cost drugs by building co-payment incentives into their formularies and by encouraging the use of mail-order delivery, where more favorable discounts may be available.

Mail-order dispensing. On behalf of its clients, Medco operates a large mail-order pharmacy (the **Medco By Mail** pharmacy), which dispensed more than 87 million prescriptions during 2005. Over the past few years, many Medco clients have implemented retail refill allowance programs to promote the use of mail order. These programs limit the number of refills of maintenance medications that members may purchase at standard retail cost-share levels; retail refills beyond this limit may require higher co-payments. These programs have stimulated an increase in the use of mail-order service, which generally benefits both members (through lower co-payments or coinsurance) and plan sponsors (through improved discounts).

Cost sharing. Member cost sharing is generally achieved through premium payments, deductibles, co-payments, and coinsurance. During 2005, the average shift in cost share was relatively small, and it had little overall effect on price inflation.

FIRST-TIME GENERICS

Over the past few years, many new generic drugs have become available due to patent expirations, at-risk launches, or successful patent challenges. These first-time generics provide a significant opportunity to reduce unit cost, since generic drugs typically cost 30% to 60% less than their brand-name counterparts.[19] By promoting use of the new generics, benefit plans can achieve a one-time savings in the first year and sustained savings in the years that follow.

New generics in 2005

The primary generic drug introductions during 2005 are shown in Table 3. 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.

Products with large market share provide the best opportunities for ongoing cost savings through generic substitution. In 2005, the best opportunities for cost reduction were the generic conversions of *Duragesic*® (fentanyl) patch, *OxyContin*® (oxycodone) tablets, *Allegra*® (fexofenadine) tablets, and *Zithromax*® (azithromycin) tablets.

Table 3. First-time generic drugs introduced during 2005
Source: U.S. Food and Drug Administration[20]; IMS

Generic approval	Brand name and dosage form	Generic name	Use	Market sales in 2004 ($M)[a]
1Q 2005	*Sporanox*® capsules[b]	itraconazole	Fungal infections	$132 (capsules only)
	Duragesic® patch	fentanyl transdermal system	Chronic pain	$1,395
2Q 2005	*Ultracet*® tablets	tramadol + acetaminophen	Acute pain	$331
	TriCor® tablets[c]	fenofibrate	Hyperlipidemia	$712
	Biaxin® tablets	clarithromycin	Bacterial infections	$198
	Lamictal® chewable tablets	lamotrigine	Epilepsy	$847
	OxyContin® tablets[d]	oxycodone (10 mg, 20 mg, 40 mg)	Chronic pain	$1,888
3Q 2005	*DDAVP*® tablets	desmopressin	Diabetes insipidus, nighttime bedwetting	$172 (tablets only)
	Arava® tablets	leflunomide	Rheumatoid arthritis	$175
	Allegra® tablets	fexofenadine	Seasonal allergic rhinitis	$1,296
4Q 2005	*Amaryl*® tablets	glimepiride	Diabetes	$276
	Zithromax® tablets	azithromycin	Bacterial infections	$1,409
	Cefzil® tablets	cefprozil	Bacterial infections	$255
	Copegus® tablets	ribavirin	Hepatitis C	$200
	Zonegran® capsules	zonisamide	Epilepsy	$148

Note: The table shows first-time generics launched in 2005 with prior-year market sales greater than $125 million. For a complete list of new first-time generics, please visit the Office of Generic Drugs website at http://www.fda.gov/cder/ogd/. FDA approval may not imply generic availability.

[a] Dollar amount reflects combined sales of all strengths and formulations of the product, unless otherwise indicated.

[b] Generic version of *Sporanox* (itraconazole) was approved in May 2004 and launched in February 2005.

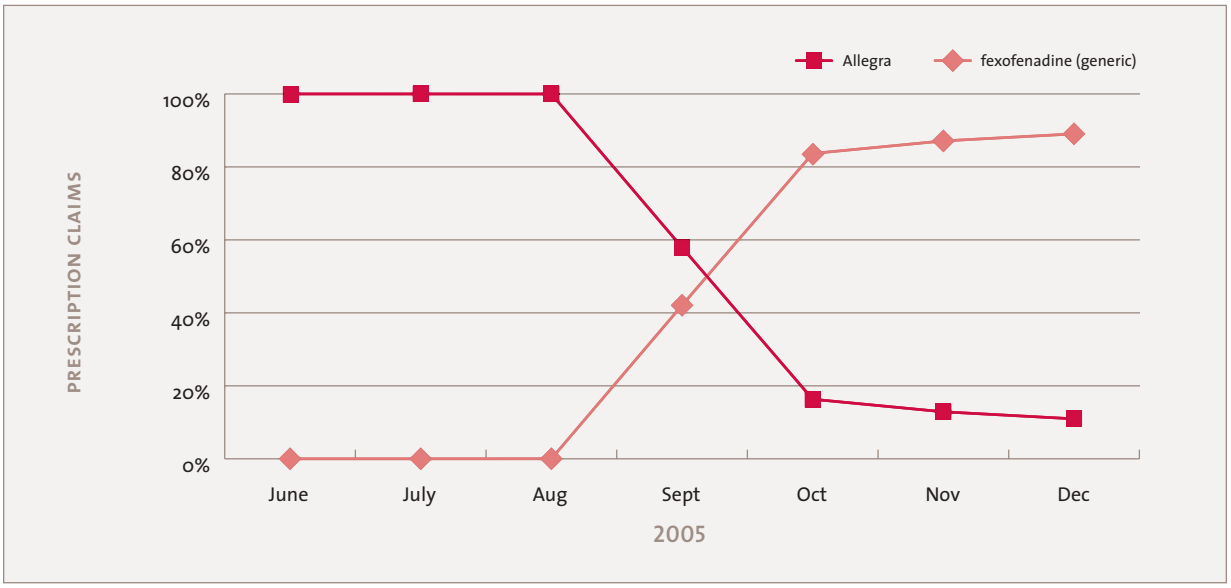
[c] *TriCor* brand-name product strengths have been reformulated from 54 mg and 160 mg to 48 mg and 145 mg, respectively.

[d] Generic version of *OxyContin* (oxycodone) was approved in March 2004; 80-mg strength was launched at-risk in March 2004; 10-, 20-, and 40-mg strengths were launched in June 2005.

Cost savings from new generics

Changes in drug selection can occur very rapidly following the introduction of a first-time generic. For example, when generic versions of *Allegra* (fexofenadine) tablets became available in September 2005, prescription volumes for the brand-name drug dropped off rapidly as the new generic drug became the dominant choice (Figure 6). *Allegra* is a widely used nonsedating antihistamine with market sales of $1.3 billion in 2004. By October 2005 (the first full month following generic availability), the brand-name product lost 84% of its overall market share to the new generics—81% at retail and 95% at mail.

Figure 6. Impact of first-time generics on *Allegra*® prescription volumes
Source: Medco data



Note: The figure shows the relative prescription volumes for *Allegra* and generic fexofenadine tablets (30 mg, 60 mg, and 180 mg). The generic tablets became available in September 2005. Data are prescription volumes for retail and mail combined. In October 2005, the generic substitution rate was 95% at mail and 81% at retail.

The changeover to a new generic can have a significant impact on unit costs during the year of the transition, and it can have a continuing impact on unit costs in following years. For example, the combined unit costs for *Diflucan*® and generic fluconazole (introduced in August 2004) were about 16% lower in 2004 than in 2003. Unit costs dropped further in 2005, the first full year of generic availability; the combined unit costs for *Diflucan* and generic fluconazole were 76% lower in 2005 than in 2004.

The impact of a new generic may be reduced if prices for the original brand-name drug are raised before the generic drug is introduced. The availability of generic fexofenadine had little net effect on unit costs for prescription antihistamines in 2005, because the transition occurred relatively late in the year and its impact was diluted by price inflation for the brand-name drug earlier in the year.

Over the past few years, the speed of the market transitions to first-time generics has increased dramatically. It is not uncommon now for a patented drug to lose 80% to 90% of its market share in a few weeks. The transition to a new generic generally occurs more quickly at mail (compared to retail), because generic interchange programs are an integral part of prescription processing by Medco's mail-order pharmacy. During 2005, the mail-order pharmacy achieved a generic substitution rate of 93% within the first month following the introduction of new generic products.

Increasing generic use

Using a variety of plan design features and other programs, Medco clients have had a major impact on generic utilization. For a large set of integrated clients (clients with both mail and retail benefits), generic substitution rates averaged over 94% during 2005. This had a large effect on therapy mix in many therapeutic classes, and unit-cost growth slowed significantly as a result (Figure 5). The use of generics has increased in response to several initiatives, including co-payment incentives, therapeutic interchange programs, and physician education programs.

GENERICS HELP BUILD STRONG PLANS SIX WAYS

Generic drugs have the following potential benefits (when used as part of a well-balanced benefit plan):

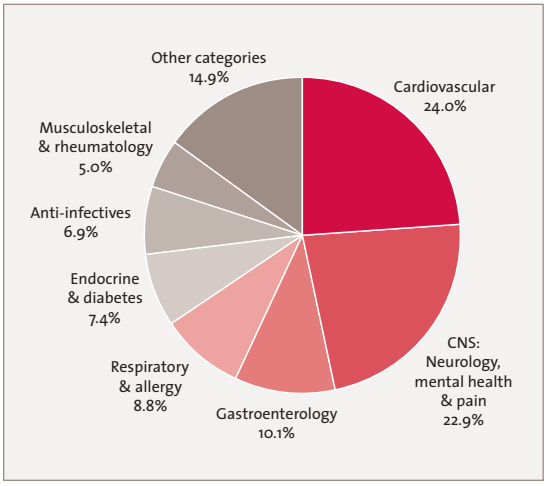
1. **Generic drugs generally cost less than their brand-name counterparts.** They provide the same efficacy and safety at a lower unit cost.
2. **Costs for generic drugs generally increase more slowly than for brand-name drugs.** During 2005, the average price inflation for generic drugs was only 0.3%, and unit costs for many generic drugs actually declined. In contrast, the average price inflation for brand-name drugs was 6.3%.
3. **Deeper discounts are generally available for generic drugs than for brand-name drugs.** These discounts off wholesale prices help control price inflation.
4. **First-time generics can lower costs during the year they are introduced.** Capitalizing on this opportunity requires an efficient process for generic substitution.
5. **The cost savings from generics can increase on a compounded basis.** Since annual inflation rates tend to be lower for generic drugs, the price difference relative to brand-name drugs may widen over time.
6. **Generics can be a low-cost alternative to other brand-name drugs in the same therapeutic class.** Where clinically appropriate, generics may provide a low-cost alternative to single-source brands (drugs that are only available in brand-name form).

Therapeutics of trend

Drug spending in 2005 was dominated by a few broad therapeutic categories (Figure 7): cardiovascular, central nervous system (CNS), gastroenterology, respiratory/allergy, endocrine/diabetes, anti-infectives, and musculoskeletal/rheumatology. These seven therapeutic categories were responsible for 85% of total drug spending during 2005.

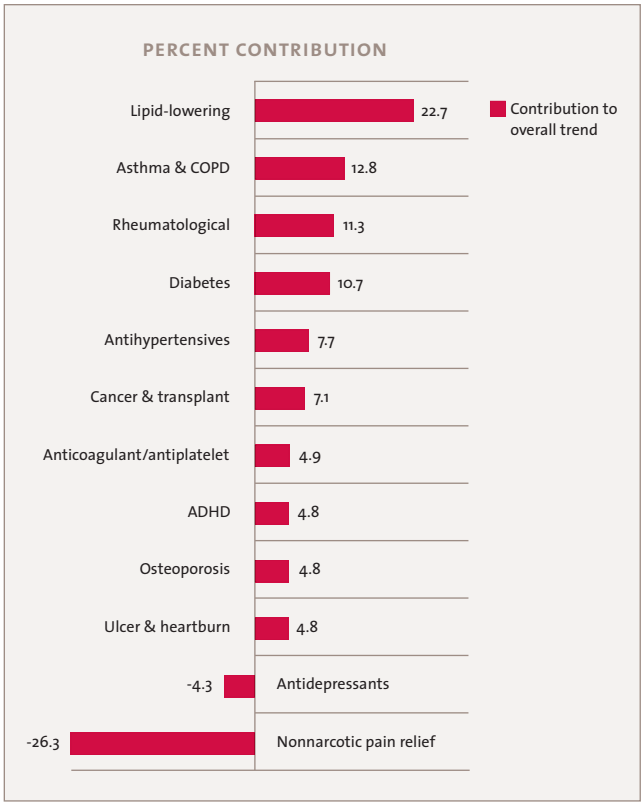
The therapeutic classes that had the largest impact on trend are shown in Figure 8. The figure shows the percent contribution of each therapeutic class to the overall trend for 2005. Spending increased for most of these therapeutic classes, but spending declines for antidepressants and nonnarcotic pain relievers helped moderate the overall trend.

Figure 7. Top therapeutic categories contributing to drug spending in 2005
Source: Medco data



Note: The figure shows the percent contribution of each therapeutic category to overall plan cost in 2005.

Figure 8. Top therapeutic classes contributing to drug trend in 2005
Source: Medco data



Note: The figure shows the contribution of each therapeutic class to overall trend in 2005. 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).

■ TOP 10 TREND DRIVERS

Ten therapeutic classes—including lipid-lowering, respiratory, and rheumatological drugs—were the strongest drivers of trend in 2005. Growth rates for these therapeutic classes are shown in Figure 9.

1. Lipid-lowering drugs

Lipid-lowering drugs continue to be the largest single driver of trend. They accounted for over 12% of net plan costs and over 22% of spending growth in 2005. Trend was driven strongly by increased sales of *Lipitor*®, a leading statin, and *Vytorin*®, a combination drug that was approved in July 2004. Trend was also driven by increased utilization of *Crestor*® (a statin, approved in August 2003), *Zetia*® (a cholesterol-absorption inhibitor, approved in October 2002), *Niaspan*® (a niacin formulation), and *TriCor*® (a fibrate).

Unit costs for lipid-lowering drugs grew slowly overall (1.3%). Although prices rose for many brand-name drugs in the class, increased use of generic lovastatin and shifts toward lower-cost brands helped offset the inflationary pressure.

Utilization of lipid-lowering drugs grew at a slower pace in 2005 (9.8%) than in 2004 (16.5%), but it continues to grow at a pace that is far above the average for prescription drugs as a whole (2.7%). Over the past few years, clinical guidelines have significantly expanded the eligible population for cholesterol-lowering therapy.[21,22] Recent clinical studies also support more aggressive cholesterol lowering for some patients, which may require the use of multiple agents.[23-26] Increased detection and prevalence of high cholesterol may also be driving growth in this therapeutic class. The use of lipid-lowering therapies increased rapidly in all adult age groups in 2005.

2. Respiratory drugs

Spending on treatments for asthma and chronic obstructive pulmonary disease (COPD) grew at a rapid pace in 2005 (16.2%). Utilization growth was led by *Advair Diskus®* and *Singulair®*, which more than offset utilization declines for some of the older controller medications. Utilization also grew rapidly for *Spiriva*, a new treatment for COPD (approved in February 2004), and for *Xolair®*, a new specialty drug for allergic asthma (approved in June 2003). Unit-cost growth was led by price increases for asthma controller medications, most of which are only available in brand-name form. Unit-cost declines for generic albuterol and ipratropium had a small moderating effect on trend.

3. Rheumatological drugs

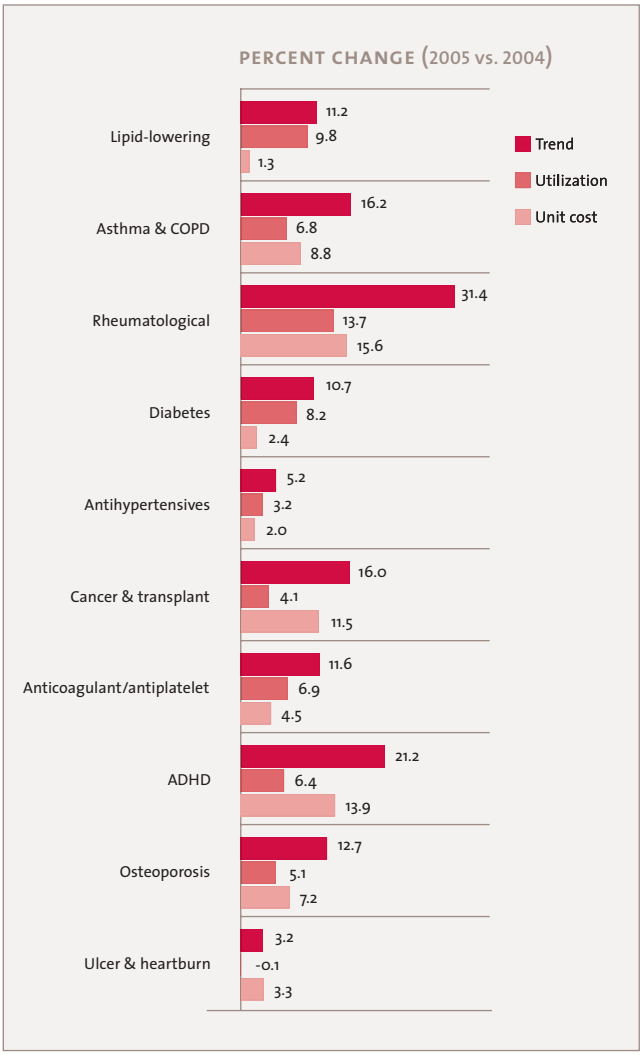
Spending for rheumatological drugs continued to grow at an exceptionally fast pace. Trend for the class was 31.4% in 2005, building on 49.5% growth in 2004. Utilization growth was primarily driven by two biologics, *Enbrel®* and *Humira®*, which are used to treat rheumatoid arthritis and an expanded set of new indications (such as psoriasis). Utilization growth was especially high for younger adults (30.2% increase, ages 20 to 34; 22.7% increase, ages 35 to 49). Unit costs grew sharply (15.6%) in this therapeutic class, which is dominated by brand-name specialty products.

4. Diabetes therapy

Spending continues to grow rapidly in this therapeutic class, which includes oral and injectable hypoglycemic medications, blood glucose monitoring equipment, and other supplies. Utilization growth continued at a strong pace for oral medications (8.1%) and insulin products (8.1%), reflecting the expanding prevalence of diabetes and the increased use of multiple-drug therapies for blood glucose control.[14] Unit-cost growth was low overall (2.4%)—the net effect of price increases for insulin products, which are only available in brand-name form, and a unit-cost decline for oral hypoglycemic products, many of which are now available in generic form.

Utilization growth for insulin products was led by newer products with faster onsets of action, including *Novolog®* (a rapid-acting insulin) and *Lantus®* (a long-

Figure 9. Top 10 trend drivers in 2005
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). Data are shown for the therapeutic classes that were the largest contributors to spending growth in 2005. Spending growth factors multiply to yield total trend, so utilization growth and unit-cost growth may not be additive.

acting basal insulin). Initial sales of *Levemir*® (insulin detemir, approved in June 2005) did not have a significant impact on 2005 trend. Utilization growth for oral medications was led by a rapid increase in the use of generic products (including metformin, glyburide, and glipizide). Brand-name thiazolidinedione products (*Actos*® and *Avandia*®) also showed strong utilization growth. Two new injectable hypoglycemic agents (*Byetta*® and *Symlin*®) were approved early in 2005, but initial sales did not have a significant impact on trend for the year.

5. Antihypertensives

Antihypertensive drugs continue to be a strong driver of trend, although the pace of spending growth in 2005 (5.2%) was slower than in 2004 (8.0%). These drugs are used to treat high blood pressure, congestive heart failure, and other cardiovascular conditions. Utilization grew most rapidly (9.8%) for angiotensin II receptor blockers (ARBs), a class of antihypertensive drugs with relatively high unit costs. Utilization also grew rapidly for beta-blockers (5.8%) and combination antihypertensive products (6.2%), while utilization of diuretics and calcium channel blockers was relatively unchanged. The use of antihypertensive drugs increased in all adult age groups; younger adults (ages 20 to 34) showed the largest increase in utilization (7.7%).

The moderate growth in unit costs (2.0%) was the net result of different patterns of pricing changes across the various classes of antihypertensive drugs. Unit costs for ACE inhibitors dropped sharply, reflecting strong price competition among these drugs, most of which are now available in generic form. Trend was also moderated by unit-cost declines for diuretics, which have long been available in generic form. These declines were more than offset by unit-cost increases for ARBs and beta-blockers. Price increases led the rapid unit-cost growth for ARBs, which are only available in brand-name form. For beta-blockers, price inflation for the leading brand-name products, *Coreg*® and *Toprol-XL*®, outweighed declining costs for generic alternatives, including atenolol and metoprolol.

6. Cancer and transplant drugs

This therapeutic class includes antineoplastics, immunosuppressants, antimetabolites, hormone therapies, and molecular target inhibitors that are used in cancer and transplant treatments. Spending in this class has accelerated rapidly over the past 3 years, increasing from an 8.7% trend in 2003 to a 16.0% trend in 2005. Utilization growth was moderate overall, but utilization grew rapidly for selected therapies, including *Gleevec*® (approved in May 2001), immunosuppressant drugs, and antiestrogens. These increases were partially offset by a sharp decline in the use of *Iressa*® (approved in May 2003), following reports that the efficacy of the drug was more limited than early data had suggested.[27] Unit costs grew rapidly (11.5%) for cancer and transplant drugs—a treatment class that is increasingly dominated by specialty medications that are only available in brand-name form.

7. Anticoagulant/antiplatelet drugs

Trend in the anticoagulant/antiplatelet class was primarily driven by increased use of *Plavix*® and *Lovenox*®. *Plavix* is an oral antiplatelet drug that is used alone or in combination with aspirin to treat acute coronary syndrome, peripheral artery disease, and other cardiovascular conditions. *Lovenox* is a specialty drug used in anticoagulation treatments; although its utilization is relatively low, its higher unit costs give it significant leverage on trend in the class. Pricing increases for the leading brand-name products in this therapeutic class were partially offset by pricing declines for generic warfarin, yielding a moderate overall increase in unit costs (4.5%).

8. Attention deficit hyperactivity disorder (ADHD) drugs

ADHD drugs have emerged as one of the leading drivers of drug trend. This therapeutic class includes CNS stimulants and nonstimulants (such as *Strattera*®) that are used to treat ADHD, narcolepsy, sleep apnea, and other CNS-based disorders. Utilization of these drugs continued to grow rapidly in 2005 (6.4%), although not as rapidly as in 2004 (14.0%). Utilization growth was strongest for extended-release formulations, such as *Concerta*® and *Adderall XR*®, which are widely prescribed for the treatment of ADHD in children and adolescents.

Trend for ADHD drugs was primarily driven by price increases for many of the brand-name products during 2005. Unit costs were moderated only slightly by price reductions for generic products. Generics are not widely used in ADHD treatment, since the nonstimulant product and most of the extended-release formulations are only available in brand-name form.

9. Osteoporosis drugs

Spending for osteoporosis treatments continued to grow rapidly in 2005 (12.7%), although not as fast as in 2004 (22.0%). Utilization growth was especially strong for two brand-name products, *Actonel*® (an oral bisphosphonate approved in May 2002 for once-weekly dosing) and *Forteo*® (an injectable product approved in November 2002). Utilization growth was also driven by increased use of *Boniva*®; a once-monthly formulation of this product was approved in March 2005. Average unit costs grew sharply (7.2%) for osteoporosis drugs, most of which are only available in brand-name form.

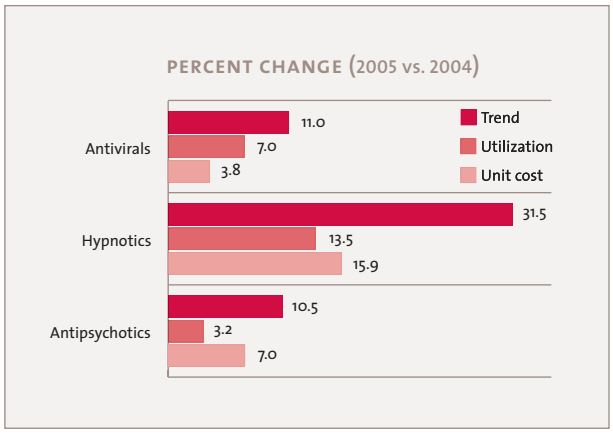
10. Ulcer and heartburn drugs

Spending for ulcer and heartburn therapies—the third-largest category of plan expense—grew 3.2% during 2005. Utilization of these prescription products declined slightly (–0.1%), and unit-cost increases were moderate overall (3.3%). Utilization of proton pump inhibitors grew at a moderate pace (3.9%), but utilization declined sharply (–22.5%) for H_2-receptor antagonists (H_2RAs). Unit-cost increases for the leading brand-name drugs were moderated by unit-cost declines for generic H_2RAs and generic *Prilosec*® (omeprazole).

FAST MOVERS

In addition to the top 10 trend drivers, several other therapeutic classes—including antivirals, hypnotics, and antipsychotics—showed rapid growth in 2005 (Figure 10). Although these "fast movers" are relatively small as a percentage of current spending, their rapid growth makes them important trend drivers to monitor and manage closely.

Figure 10. Therapeutic classes with rapid spending growth in 2005
Source: Medco data



Note: The figure shows trend data for three moderate contributors to plan spending that grew rapidly in 2005 (fast movers). Year-over-year changes are shown for plan cost (drug trend), utilization (days per eligible), and unit cost (cost per day).

Antivirals

Spending on antiviral drugs grew at a rapid pace in 2005 (11.0%). Spending growth was especially strong for *Truvada*®, an antiretroviral treatment for HIV/AIDS, and *Valtrex*®, a treatment for herpes zoster (shingles), genital herpes, and cold sores. Drug trend for antivirals was also driven by a sharp increase in sales of *Tamiflu*®, which is indicated for the prevention and treatment of influenza. The unusual sales growth for *Tamiflu* was not associated with the flu season, which was relatively mild, but was a response to public concerns throughout 2005 about the possibility of a bird-flu pandemic. Dispensing limits and manufacturer supply restrictions were introduced during the year to help ensure that supplies of *Tamiflu* would be available to treat seasonal influenza.

Hypnotics

Spending growth for sedative-hypnotic drugs was exceptionally high in 2005 (31.5%)—higher than for any other therapeutic class. Growth was primarily driven by sales of the leading brand-name product, *Ambien*®, and by strong first-year sales of *Lunesta* (approved in December 2004). Unit-cost growth was very high (15.9%), reflecting price increases and changes in therapy mix among brand-name drugs in the class. Price declines for generic temazepam had only a slight moderating effect on the rapid growth in unit costs. Utilization of sedative-hypnotics grew rapidly in all adult age groups; growth was especially rapid for younger adults (ages 20 to 34).

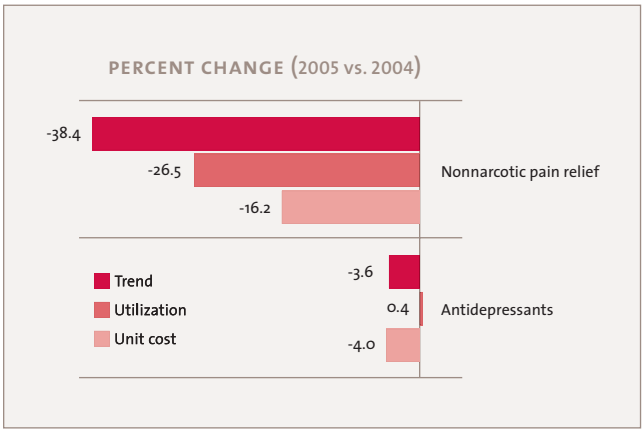
Antipsychotics

The rapid growth in spending for antipsychotics was driven by a sharp increase in unit costs (7.0%), reflecting price increases for brand-name medications, which dominate prescribing in this class. Although utilization growth was moderate overall (3.2%), utilization increased rapidly for some medications (such as *Abilify*®, *Geodon*®, and *Seroquel*®) and declined for others (such as *Zyprexa*®). These changes in therapy mix may reflect heightened awareness of safety issues following publication of a major comparative study on the safety and efficacy of antipsychotic medications.[28]

■ NEGATIVE TREND DRIVERS

Two therapeutic classes—nonnarcotic pain relievers and antidepressants—showed large spending declines and were significant decelerators of trend in 2005 (Figure 11).

Figure 11. Therapeutic classes with negative trend in 2005
Source: Medco data



Note: The figure shows trend data for the two therapeutic classes with the largest declines in plan spending in 2005 (negative trend drivers). Year-over-year changes are shown for plan cost (drug trend), utilization (days per eligible), and unit cost (cost per day).

Nonnarcotic pain relievers

Spending for nonnarcotic pain relievers declined dramatically in 2005 (–38.4%). This therapeutic class includes the traditional nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen, and the COX-2 inhibitors. Utilization dropped sharply (–26.5%), reflecting increased safety concerns and new warning labels that applied to all drugs in the class.[8,9]

The utilization decline for the COX-2 inhibitors was especially dramatic on a year-over-year basis (–65.0%). This decline was largely due to the market withdrawals of *Vioxx* in September 2004 and *Bextra* in April 2005, but it also reflects a significant reduction in the use of *Celebrex* (the only remaining COX-2 inhibitor on the market). The utilization of traditional NSAIDs increased on a year-over-year basis (37.2%), as some users of COX-2 inhibitors shifted to alternative products. The net effect of all these changes has been a major shift in therapy mix—COX-2 inhibitors accounted for 60% of therapy days in 2004, but only 28% of therapy days in 2005.

The shift in therapy mix toward traditional NSAIDs contributed to a large decline in unit costs for nonnarcotic pain relievers (–16.2%). Most of the traditional NSAIDs are available in generic form, and unit costs for these products have historically been well below the unit costs of the COX-2 inhibitors. However, that pricing disparity narrowed in 2005, as prices for some of the traditional NSAIDs began to increase, and utilization shifted toward *Mobic*®, a traditional NSAID product that is only available in brand-name form.

Antidepressants

Spending for antidepressant medications declined in 2005 (–3.6%), which helped moderate drug trend overall. Utilization was essentially unchanged on a year-over-year basis, but there were some significant shifts in therapy mix within the class. The utilization of selective serotonin reuptake inhibitors (SSRIs) declined 2.8%, and most SSRIs (except *Lexapro*®) participated in this decline. Utilization increased for the class of "miscellaneous antidepressants," which includes the serotonin-norepinephrine reuptake inhibitors (SNRIs) and *Wellbutrin*® (buproprion). Utilization growth in this class was led by *Cymbalta*, a new SNRI that was approved in 2004 for two indications—treatment of depression and management of neuropathic pain associated with diabetes.

The unit-cost decline for antidepressants in 2005 (–4.0%) was primarily due to competitive price reductions for generic SSRIs. Generic citalopram (*Celexa®*) drove the largest decline in unit costs; this generic product was approved in October 2004, so 2005 was its first full year of availability.

Over the past few years, utilization of antidepressants has been moderated by safety concerns surrounding the use of these products by both adults and children.[6,7] In October 2004, the FDA mandated the addition of black box warnings for all antidepressant products regarding the risk of increased suicidality in children, especially during the first few months of treatment.[6,29] The FDA is currently reviewing data regarding a possible increased risk of suicidality in adults during treatment with antidepressant medications.[7]

Specialty drug trend: The leading edge

Pharmacy spending for specialty drugs continued to grow at a rapid pace in 2005. These drugs are used to treat a broad array of complex diseases, including rheumatoid arthritis, hemophilia, cancer, hepatitis C, anemia, cystic fibrosis, and growth hormone deficiency. Several new specialty drugs were introduced in 2005 (Table 1), and many drugs in this class received approval for new or expanded indications (Table 2). Specialty drugs generally require special handling, administration by infusion or injection, or specialized patient support.

This section provides an overview of spending patterns for specialty drugs that were purchased under the pharmacy benefit. To obtain a more complete picture of specialty drug spending, costs under the pharmacy benefit need to be combined with costs that are incurred under the medical benefit. For some plan sponsors, up to 70% of specialty drug spending may be billed under the medical benefit. Medications that are often self-administered (such as treatments for hepatitis C) are more likely to be billed under the pharmacy plan, while infused products (such as treatments for anemia) are more likely to be billed under the medical plan.

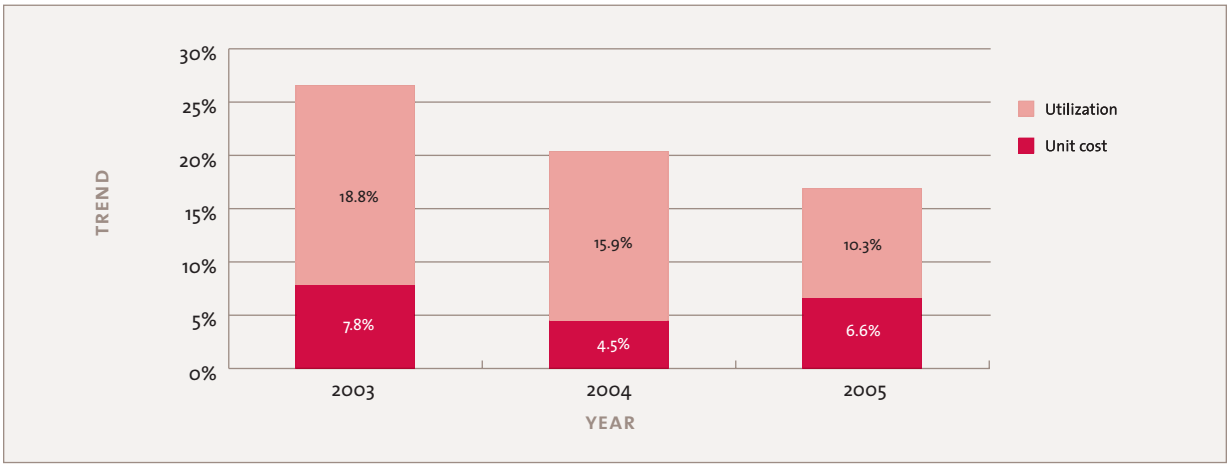
SPENDING GROWTH

Specialty drugs are a significant component of pharmacy spending and a major driver of spending growth. Specialty drugs accounted for 9.7% of total pharmacy spending in 2005, up from 8.5% in 2004.

Specialty drug spending grew by 16.9% in 2005—significantly faster than the 5.4% average trend for drug spending as a whole. This powerful trend driver could easily be missed in a conventional analysis by therapeutic class, since specialty drugs are scattered across many therapeutic categories. The spending growth for specialty drugs accounted for 25.1% of the total growth in drug spending in 2005. Specialty drugs are now the largest therapeutic segment driving drug trend—larger than lipid-lowering drugs, which accounted for 22.7% of trend.

Although trend for specialty drugs remains high, the pace of growth has slowed over the past 3 years (Figure 12). Annual spending growth has declined from 26.6% in 2003 to 16.9% in 2005. Utilization growth has shown a consistent decline, moderating from 18.8% in 2003 to 10.3% in 2005. Unit-cost growth has been more variable, reflecting year-to-year variations in average price inflation. Pharmacy spending as a whole has shown a progressive unit-cost decline, which is primarily due to a shift in therapy mix toward generic drugs (Figure 5). This progressive pattern of unit-cost decline is not mirrored in the specialty drug class, where generic options are not generally available.

Figure 12. Specialty drug trend under the pharmacy benefit (2003-2005)
Source: Medco data



Note: The figure shows the contributions of utilization growth and unit-cost growth to total trend for specialty drugs under the pharmacy benefit. Trend is the percent change in plan spending compared with the prior year.

The rapid growth in specialty drug spending is primarily due to a large increase in utilization. Utilization of specialty drugs grew 10.3% in 2005, far exceeding the average utilization growth of 2.7% 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.

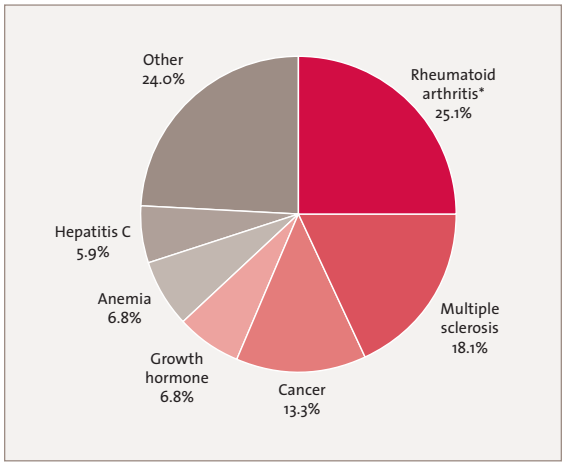
Unit costs for specialty drugs increased by 6.6% during 2005; this is significantly higher than the 2.7% increase for prescription drugs as a whole. The unit-cost growth is primarily due to AWP price inflation for many of the specialty products. Therapy mix changes are limited for specialty drugs, since there are often few therapeutic alternatives for these drugs and even fewer generic alternatives. Some of the older biotech drugs (such as human growth hormone) are not patent-protected; however, the FDA has not yet defined a regulatory framework for approving biogeneric alternatives.

SPECIALTY GROWTH DRIVERS

There were wide variations in spending patterns across the specialty drug classes in 2005. Over 75% of the spending on specialty drugs was concentrated in a few therapeutic areas—rheumatoid arthritis, multiple sclerosis (MS), cancer, growth hormone deficiency, anemia, and hepatitis C (Figure 13).

The growth in pharmacy spending for specialty drugs was also concentrated in a small number of therapeutic areas (Figure 14). Spending increases were highest for drugs used to treat rheumatoid arthritis, cancer, MS, osteoporosis, deep vein thrombosis (DVT), and growth hormone deficiency. Trend was moderated by spending declines in treatments for hepatitis C, immune deficiency, and infertility.

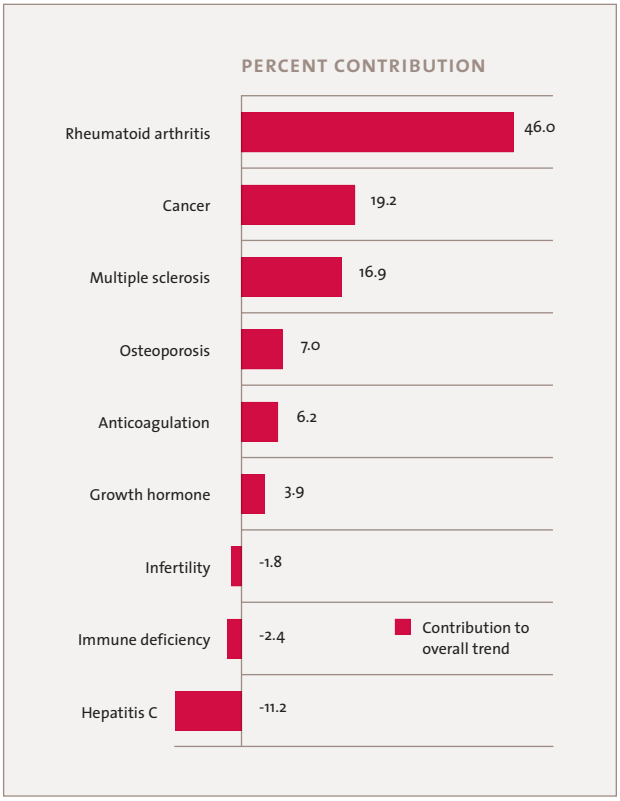
Figure 13. Top therapeutic classes contributing to pharmacy spending for specialty drugs in 2005
Source: Medco data



Note: The figure shows the percent contribution of each therapeutic class to pharmacy spending for specialty drugs in 2005.

* The drugs in this class may also be used to treat plaque psoriasis, Crohn's disease, ankylosing spondylitis, and other conditions.

Figure 14. Top therapeutic classes contributing to specialty drug trend under the pharmacy benefit in 2005
Source: Medco data



Note: The figure shows the contribution of each therapeutic class to the overall trend for specialty drugs in 2005. 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). Data are expressed as a percentage of the total increase in plan cost.

TOP SIX TREND DRIVERS

Growth rates for the top six drivers of specialty trend are shown in Figure 15. Unit-cost growth was a prominent contributor to trend in many of these specialty drug classes.

- **Rheumatoid arthritis.** Spending growth was especially high (35.7%) for the class of drugs used to treat rheumatoid arthritis, plaque psoriasis, and Crohn's disease. Utilization increased rapidly for most treatments in this class, including *Enbrel*, *Humira*, and *Remicade*®. Over the past few years, these products have been approved for an expanding set of indications (see Table 2 for new indications in 2005). Increased dosing frequency and expanded off-label use have also contributed to increased utilization of these products.

- **Cancer.** Spending growth for cancer treatments was fueled by price inflation and shifts in product mix, resulting in exceptionally fast unit-cost growth in 2005 (21.6%). Utilization of cancer treatments grew moderately overall (3.8%). *Tarceva*®, a new oral treatment for non–small-cell lung cancer (approved in November 2004), was a significant driver of trend. Utilization of *Tarceva* grew rapidly in 2005, its first full year of sales. *Tarceva* was approved for a new indication, treatment of advanced pancreatic cancer, in November 2005.

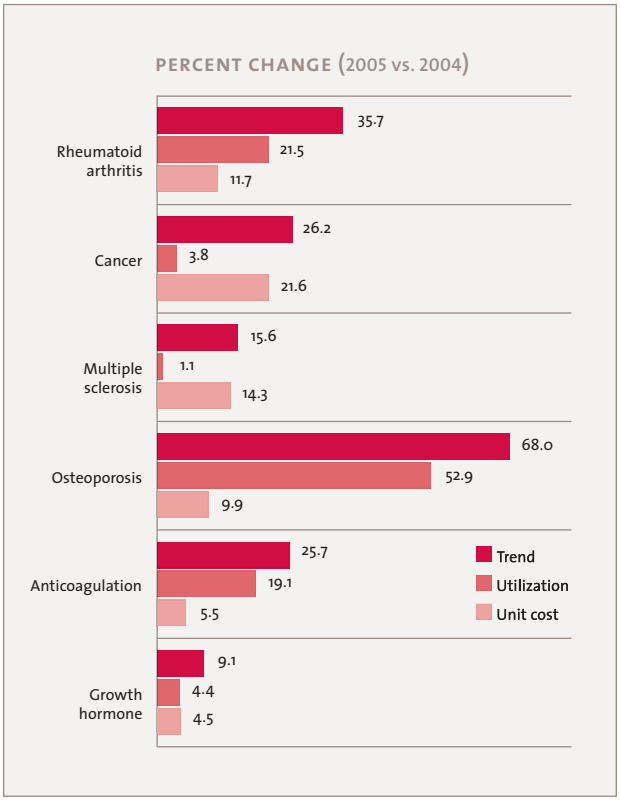
- **Multiple sclerosis.** The rapid trend for MS treatments was primarily due to price inflation for the leading brand-name products. Unit costs for the class rose 14.3% overall.

- **Osteoporosis.** Utilization of *Forteo* increased by more than 50% in 2005. *Forteo*, a high-cost injectable treatment for osteoporosis, was approved in November 2002.

- **Anticoagulation.** Trend for DVT/anticoagulation treatments was led by rapid utilization growth for *Lovenox*.

- **Growth hormone deficiency.** The use of growth hormone treatments grew at a more moderate pace in 2005 (4.4%) than in 2004 (11.3%). Unit costs increased 4.5% in response to price increases for the leading products.

Figure 15. Top six drivers of specialty drug trend in 2005
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). Therapeutic classes are rank-ordered from the largest contributor to trend (at the top) to the smallest contributor (at the bottom). Spending growth factors multiply to yield total trend, so utilization growth and unit-cost growth may not be additive.

FAST MOVERS

Specialty trend was also driven by several "fast movers"—drug classes that account for a small fraction of specialty drug spending, but show exceptionally rapid spending growth:

- **Pulmonary arterial hypertension.** Spending for these treatments grew rapidly (38.9%) in 2005, led by growth in utilization and unit costs for *Tracleer®*. Initial sales of *Ventavis®* (approved in December 2004) and *Revatio®* (approved in June 2005) also contributed to trend in this class. Utilization growth has been stimulated by the increased use of combination therapy for this condition.
- **Asthma.** Utilization of *Xolair* increased almost 50% on a year-over-year basis. *Xolair*, the only specialty drug in this class, was approved in June 2003 for the treatment of allergic asthma.
- **Hyperparathyroidism.** Utilization of *Sensipar®* grew rapidly in 2005, its first full year of sales. *Sensipar*, an oral treatment for certain forms of hyperparathyroidism, was approved in March 2004.
- **Psoriasis.** This specialty drug class includes *Raptiva®* and *Amevive®*. Utilization in the class increased by almost 50% in 2005, led by a rapid increase in sales of *Raptiva*.

NEGATIVE TREND DRIVERS

Spending declines in a few specialty drug classes helped moderate the overall trend. Hepatitis C treatments showed a large decline in spending (–21.4%), which was the net result of a large decrease in utilization (–22.2%) and moderate growth in unit costs (1.0%). The utilization decline reflects the impact of initiatives to manage hepatitis C treatment durations to levels that are consistent with clinical guidelines. Increased use of generic ribavirin products helped moderate unit-cost growth, offsetting price inflation for some brand-name products in the class.

Lower utilization of *Actimmune®* led an overall spending decline for immune deficiency treatments (–18.8%); utilization of this product for off-label indications, such as idiopathic pulmonary fibrosis, has become more selective. Spending also declined for infertility treatments (–7.5%), reflecting changes in therapy mix and a net reduction in unit costs.

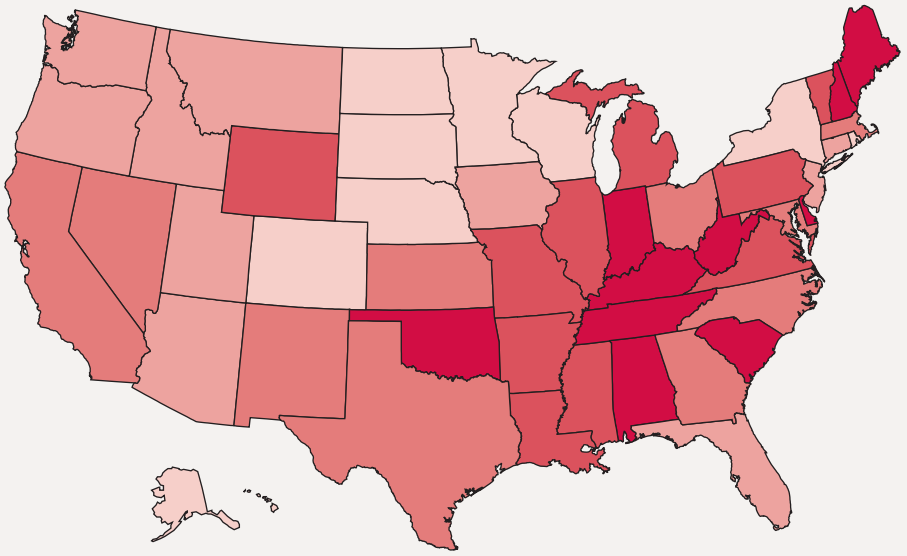
Demographics of trend

Prescription drug use varies markedly by age group, gender, geographic region, and many other sociodemographic factors. Some of this variation is due to differences in disease prevalence and treatment-seeking behavior, but some may also result from differences in how medication treatment is targeted toward specific groups of patients. FDA-approved drug indications are frequently limited to specific age groups, and product guidelines often vary dosing based on individual variables such as body weight, blood test results, or other markers. As medication treatment becomes more personalized, utilization and trend will be driven more directly by the demographic and pharmacogenetic profiles of plan members.

■ GEOGRAPHIC PROFILE

Prescription drug utilization rates vary widely across the United States (Figure 16). In 2005, utilization levels were more than 35% higher in the 10 states that had the highest utilization per member, compared with the 10 states that had the lowest utilization. These regional variations reflect differences in demographics, benefit plan mix, disease prevalence, care-seeking behavior, physician prescribing, and other factors. In high-utilization states, therapy days per member were especially high in several therapeutic categories, including antihypertensive, lipid-lowering, antidepressant, diabetes, and ulcer/heartburn medications.

Figure 16. Drug utilization by state in 2005
Source: Medco data



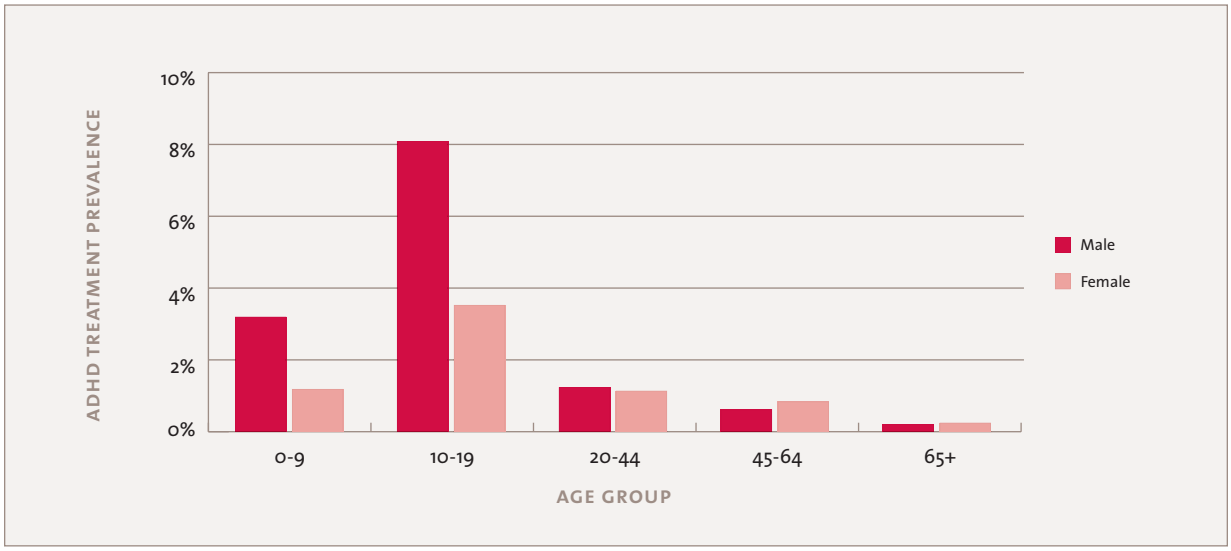
LEVEL OF UTILIZATION	STATES	AVERAGE THERAPY DAYS
Highest	DE, KY, AL, TN, OK, SC, ME, IN, WV, NH	508-670
High	PA, VA, LA, VT, MS, AR, MO, WY, IL, MI	460-507
Medium	NC, MD, TX, NV, GA, MA, OH, CA, NM, KS	418-452
Low	UT, AZ, CT, ID, NJ, FL, WA, OR, IA, MT	381-409
Lowest	RI, NY, CO, SD, WI, ND, MN, NE, AK, HI	252-375

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.

GENDER PROFILE

The gender profile of medication use varies widely by therapeutic class and treated condition. For example, there are significant variations by age and gender in the use of medication treatments for ADHD (Figure 17). Treatment prevalence is significantly higher among children than adults, which may reflect lower prevalence or underdiagnosis of the condition in adults.[30,31] Among children, treatment rates are significantly higher for boys than for girls, which may also reflect different prevalence rates or diagnostic rates in some combination. There is growing evidence that genetic markers can be used to predict a patient's response to specific ADHD medications, such as methylphenidate.[32] In coming years, the therapy mix (and trend) for ADHD medications may be guided by the results of genetic testing.

Figure 17. Prevalence of ADHD medication use by age group and sex (2005)
Source: Medco data



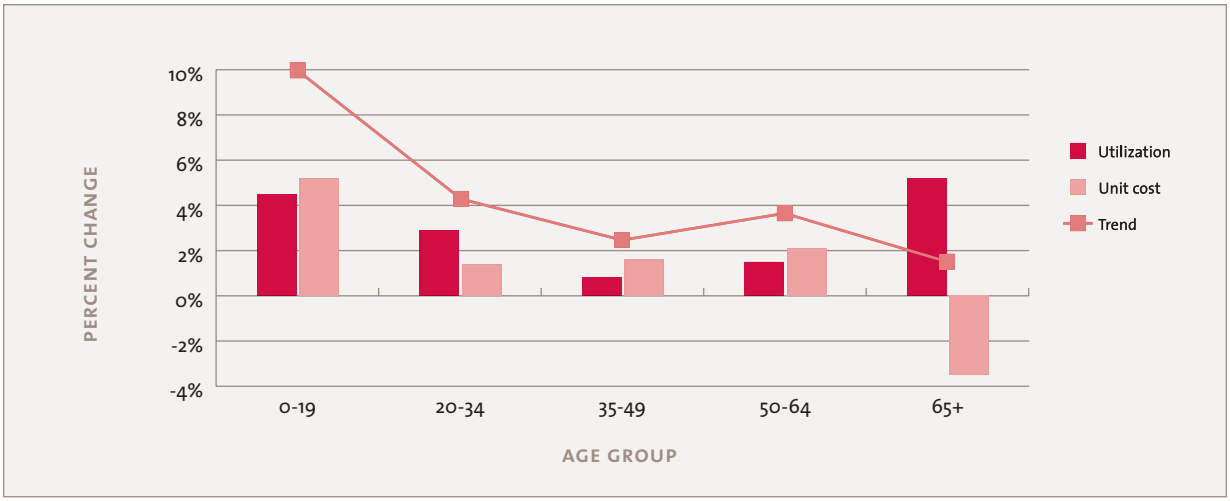
Note: For each age group, the figure shows the percentage of members who received one or more prescriptions for ADHD medications during 2005.

AGE GROUP PROFILE

Drug utilization varied widely by age group in 2005. Seniors continued to show the highest level of utilization per member, and children showed the lowest. Although seniors comprised only 17% of plan members in 2005, they accounted for 41% of prescription drug utilization.

Spending growth also widely varied by age group, as shown in Figure 18. Trend was highest for children (9.9%), and lowest for seniors (1.5%). These trend rates are the net effect of very different patterns of utilization growth and unit-cost growth for the different age groups. Utilization grew rapidly for children (4.5%) and for seniors (5.2%), but the unit costs associated with this growth were very different. For children, the use of brand-name medications (often for acute conditions) is more common, and unit costs for their product mix increased. For seniors, the use of generic medications (often for chronic conditions) is more common; unit costs for their product mix decreased, offsetting most of the growth in utilization.

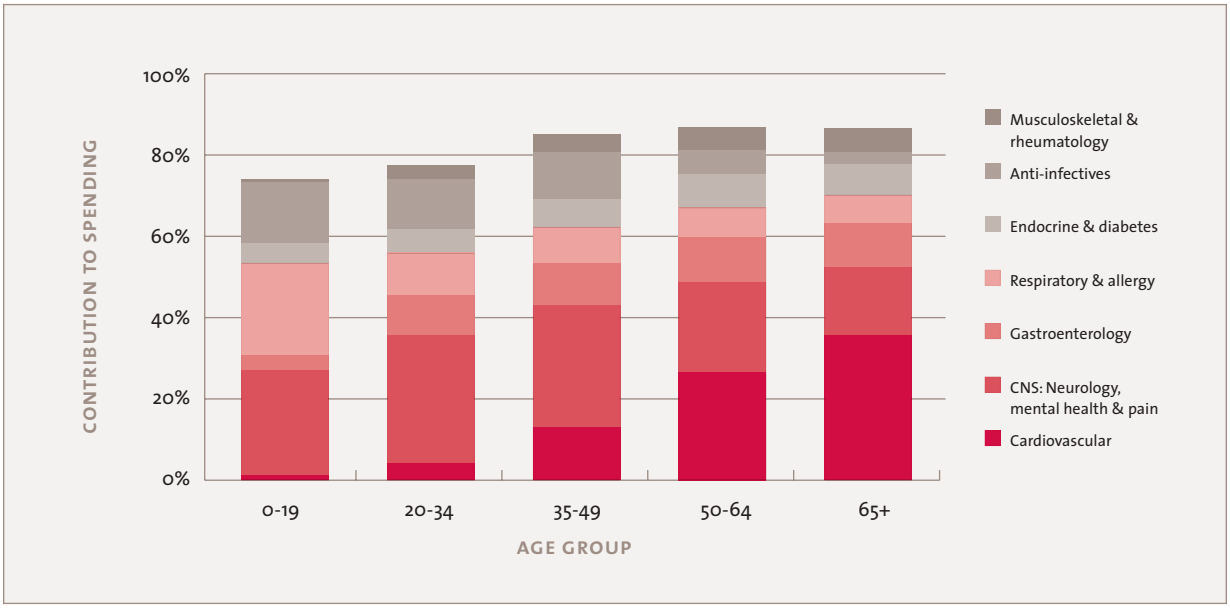
Figure 18. Drug trend by age group in 2005
Source: Medco data



Note: The figure shows the contributions of utilization growth and unit-cost growth to overall trend for each age group. The Y axis shows the percent change in each measure compared with the prior year. Utilization is the average number of therapy days per member per month (PMPM). Unit cost is the average cost per day of therapy. Trend is the change in average plan cost PMPM.

The primary types of drug purchases vary widely by age group, reflecting the different medical conditions that predominate in each group (Figure 19). Children primarily take medications for respiratory conditions (including asthma and allergies), neurological and behavioral disorders, and infections. For younger adult age groups (ages 20 to 49), CNS drugs account for the largest share of drug spending. For seniors (age 65 and older), the most commonly used medications are for cardiovascular conditions, including high cholesterol, high blood pressure, and heart failure.

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



Note: For the top seven categories of spending in 2005, 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.

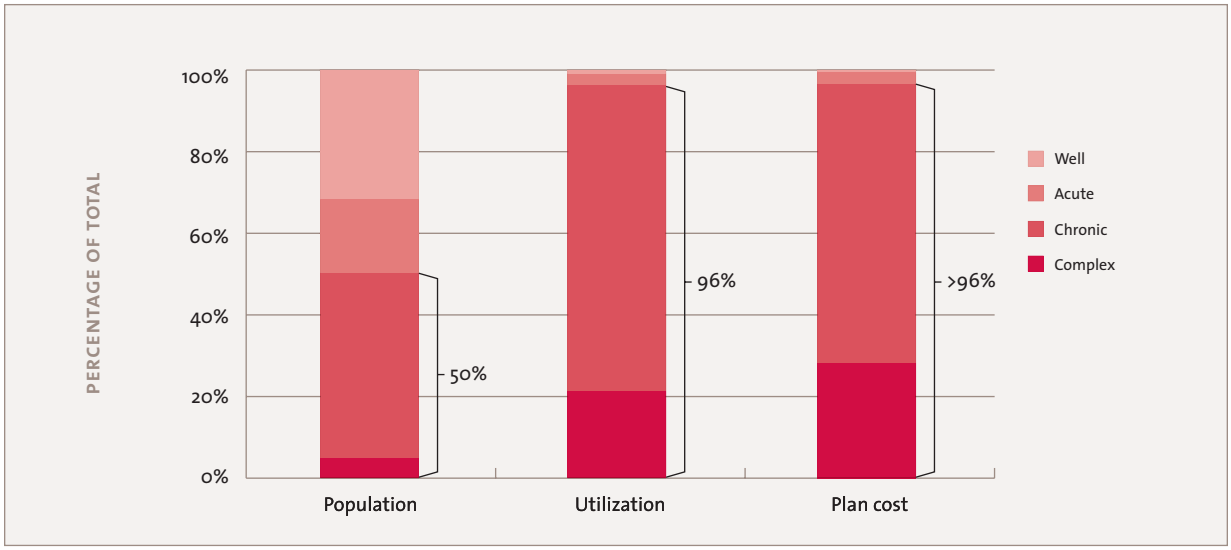
THERAPEUTIC PROFILE

About 50% of plan members have chronic or complex conditions for which they receive medication treatment. These patient groups account for a disproportionate share of utilization and cost in prescription benefit plans (Figure 20):

- **Complex patient group.** Patients in the *complex group* use medications to treat complex medical conditions (such as heart failure) or multiple chronic conditions (such as diabetes and cardiovascular disease). These patients represent only 5% of the population, but they account for 21% of total utilization and 28% of annual costs.
- **Chronic patient group.** Patients in the *chronic group* use medications to treat individual chronic conditions, such as high cholesterol, high blood pressure, arthritis, or back pain. These patients represent about 45% of the population, but they account for 75% of utilization and over 68% of annual costs.
- **Acute and well patient groups.** The remaining 50% of plan members (those with only occasional or acute need for medications) account for only 4% of utilization and less than 4% of the total costs. Patients in the *acute group* use medications to treat such conditions as colds and flu, bacterial infections, or minor injuries. Patients in the *well group* use no medications, or they use vitamins, oral contraceptives, or medications for conditions such as acne.

The chronic and complex patient groups provide the greatest opportunity to help manage costs and improve the focus and quality of care.

Figure 20. Spending and utilization for four therapeutic groups (2005)
Source: Medco data



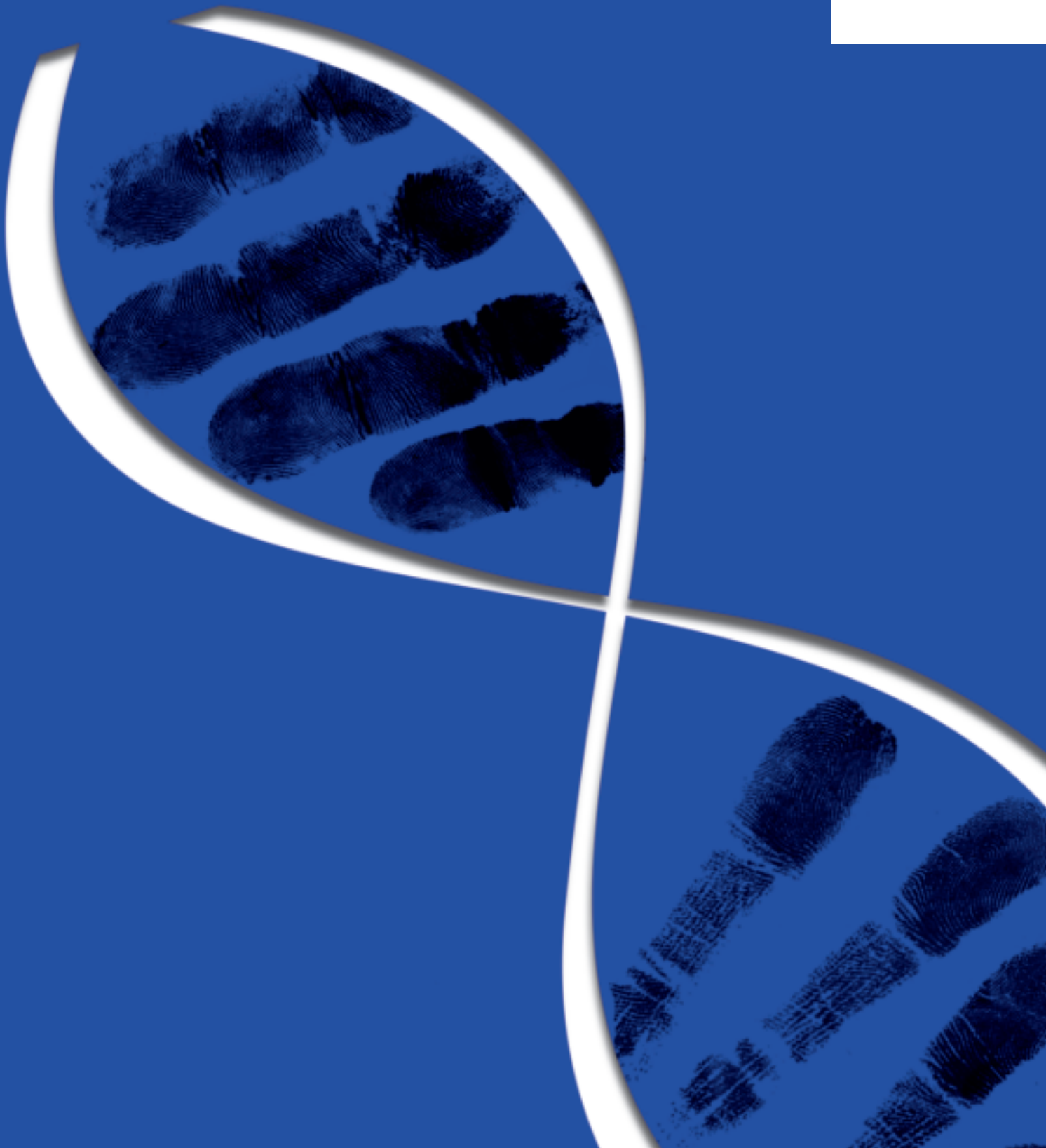
PHARMACOGENETIC PROFILE

In the future, the selection of drug treatments is likely to be based increasingly on a patient's genetic profile. Patterns of genetic variations will help identify the treatments that are more likely to be effective in individual patients, or less likely to cause serious side effects.[33,34] To date, the use of pharmacogenetic tests in clinical practice has been limited, so it has had only a small impact on patterns of drug utilization and trend. However, as clinical genetics becomes more commonplace, utilization and cost will be driven much more directly by major pharmacogenetic groups in a plan population.

Some genetic variations affect a broad cross-section of medications in current use. For example, genotypic variations in the cytochrome P-450 2D6 (CYP2D6) enzyme, which is responsible for the metabolism of about 25% of all prescription drugs, can have a profound effect on drug action and drug response.[35] Utilization rates for many of these drugs are relatively high, so these percentages may underestimate the potential impact of these genetic variations on clinical practice. These variations may affect treatment decisions for some of the largest contributors to plan cost, including many psychiatric and cardiovascular medications.

DESIGNING THE FUTURE:
THE HELIX OF CARE

2



Today's design is the promise for tomorrow.

This section will help you:

- **Anticipate the market developments that will shape trend in coming years.** New drugs and new indications will change the therapeutic options for many conditions. Trend will be driven most strongly by cardiovascular drugs and therapeutic biologics. The launch of new generics for many leading brands will help offset the rapid cost growth for specialty drugs.

- **Understand how genetic testing will help personalize care.** Tests for genetic variations will be used to predict the safety and efficacy of drugs in individual patients. Medications will be targeted to the people who respond to them best.

Agents of change

New drugs and new indications will be significant drivers of trend over the next few years. Advances in genomics and biotechnology will produce new, high-cost drugs for the treatment of various cancers, immune disorders, retinal disease, enzyme deficiency disorders, cardiovascular disease, and diabetes. The drug pipeline includes some novel drugs that will address specific conditions or patient populations for which there are few, if any, therapeutic options today.

Several market forces will help moderate the growth in spending. The introduction of a large number of first-time generics over the next few years will have a significant moderating effect on unit-cost growth, as the product mix shifts toward generic options in many therapeutic categories. The availability of new over-the-counter (OTC) products—possibly including additional allergy medications—may reduce utilization growth in a few therapeutic categories.

Pharmacogenetic testing is an emerging field of medicine that is likely to have a significant impact on drug therapy and drug trend over the next 10 years. These laboratory tests will be used to detect genetic polymorphisms and other biomarkers that can be used to help predict drug action and drug response in each patient. Advances in clinical genetics will enable a more personalized approach to medication treatment, since drug selection may be tailored to individuals based on their unique genetic makeup. A detailed review of these developments is provided later in this section, beginning on page 60.

This section begins with an overview of what lies ahead—pipeline drugs, new indications, first-time generics—and their potential impact on trend. All of these developments present challenges and opportunities for innovative plan design and clinical management.

DRUG TREND: THE NEXT 3 YEARS

Based on existing plan designs and coverage provisions, Medco expects that the average drug trend for plan sponsors will range between 6% and 9% per year over the next 3 years (Table 1). These projections are computed at the average wholesale price (AWP) level, unadjusted for changes in discounts or cost sharing that may occur over the next few years. Measures of actual plan performance may be lower than these projections. In 2005, the AWP-based trend was 6.3%, but the average net cost trend (after adjusting for discounts and cost sharing) was 5.4%.

Table 1. Drug trend projection for 2006-2008*

Year	2006	2007	2008
Utilization increase	2% to 3%	1% to 2%	2% to 3%
Price and mix increase	5% to 6%	5% to 6%	5% to 6%
Annual total	7% to 9%	6% to 8%	7% to 9%

* Projected change in drug spending on an average wholesale price (AWP) per-member per-year (PMPY) basis.

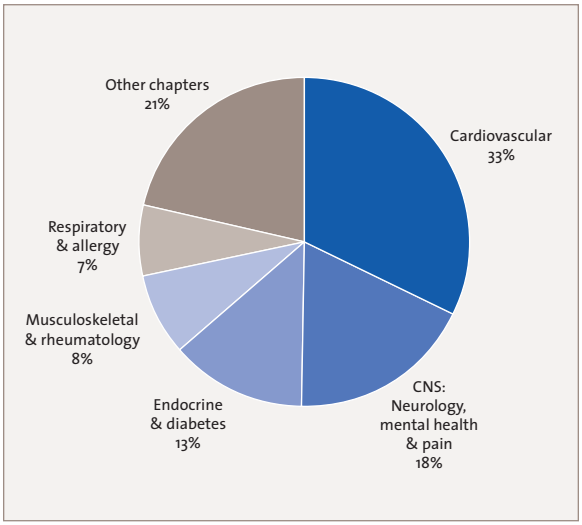
As in the past, plan sponsors with less aggressive coverage management and plan design strategies are more likely to have somewhat higher levels of drug trend. Plan sponsors that aggressively adjust coverage policies, expand incentives for generic utilization, and adjust member cost share are likely to experience lower levels of spending growth.

AWP-based unit cost is expected to grow at a faster rate than utilization over the next few years. Net unit costs (after discounts and cost sharing) will also grow, but only slightly more quickly than utilization. A primary reason for the difference between AWP trend and net cost trend is the discounting associated with generics. The net cost for generics is generally much lower than full AWP, and the availability and use of first-time generics is expected to increase rapidly over the next 3 years. In 2005, increased use of generics helped clients achieve net unit-cost growth of only 2.7%—well below the 4.7% growth in unit costs at the AWP level.

About 80% of drug trend will continue to be driven by drugs in 5 of the 16 broad chapters in the **Preferred Prescriptions®** Formulary (Figure 1). Because of the high prevalence of cardiovascular disease and the high use of cardiovascular drugs, spending growth in the cardiovascular category will continue to outpace all other areas. Detailed projections for these top five therapeutic categories are provided later in this section, beginning on page 41.

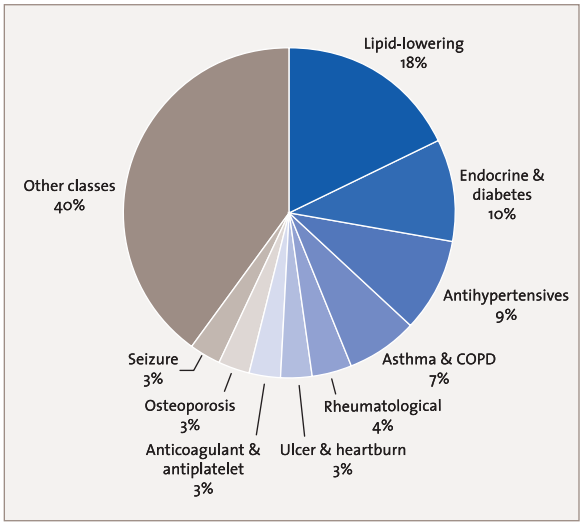
Nine specific drug classes, including lipid-lowering drugs, antihypertensives, and drugs for diabetes, will account for about 60% of the overall trend (Figure 2).

Figure 1. Top therapeutic categories contributing to projected drug trend (2006-2008)
Source: Medco projection



Note: The figure shows the five therapeutic chapters that are likely to drive the majority of spending growth between 2006 and 2008. Data are expressed as a percentage of the total projected increase in plan cost.

Figure 2. Top therapeutic classes contributing to projected drug trend (2006-2008)
Source: Medco projection



Note: The figure shows the nine therapeutic classes that are likely to drive the majority of spending growth between 2006 and 2008. Data are expressed as a percentage of the total projected increase in plan cost.

FORECASTING TREND

To develop trend projections, Medco uses a stratified, random sample of members who are representative of the entire book of business. The sample is stratified by age, gender, and geographic region. For the 2006-2008 drug trend forecast, the sample comprised about 1 million randomly selected members who were continuously eligible during the 48-month period from December 2001 through November 2005.

When developing trend projections, Medco considers many factors that are likely to affect future unit costs and utilization, including:

- New drug approvals
- New or expanded indications for existing drugs
- New dosage forms
- New combination products
- Patent expirations and first-time generics
- Possible OTC conversions
- Research findings and clinical recommendations likely to affect prescribing practices
- Changes in disease prevalence, disease recognition, or diagnostic criteria

These anticipated developments are combined with historical utilization and cost data to provide forecasts for the following components of drug trend:

Utilization—changes in the number of users, and changes in the number of days of therapy per user

Mix—changes in unit cost due to shifts in market share among generic and brand-name drugs in the same category

Price—changes in unit cost due to increases in manufacturers' prices for existing drugs

Market dynamics

NATIONAL DRUG TREND

According to estimates from the Centers for Medicare and Medicaid Services (CMS), national healthcare spending grew 7.9% in 2004, the lowest rate of increase since 2000.[1] The national growth rate for retail drug spending declined to 8.2% in 2004, which was lower than the growth rates for hospital services (8.6%) and physician services (9.0%) for the first time in many years. The slower trend for prescription drug spending was a primary reason for the slower growth in total healthcare spending in 2004.[1] CMS points to several contributors to the slower growth of drug costs at the national level, including greater use of generics, the rising popularity of tiered pharmacy benefit plans, recently introduced OTC products, safety concerns tempering the use of certain drug categories, higher than anticipated Medicaid rebates, and greater use of mail-order dispensing.[1]

CMS predicts relatively stable growth in national retail drug spending over the next 5 years, slowing to 7.7% in 2006 and then returning to the 8.0-to-8.2% range through 2010.[2,3] The spending growth rates for hospital and physician services are expected to decline from their peak in 2004. As a result, prescription drugs are likely to return to their status as the fastest-growing major segment of national healthcare expenditures.[3]

THE DRUG PIPELINE

Many potential blockbuster drugs are expected to come to market in the next few years, including new medications for diabetes, cancer, immunological diseases, obesity, and cardiovascular conditions. Although some of these drugs could reach annual sales well in excess of $1 billion, a portion of these sales for some of these drugs is likely to come from spending that would have been directed towards other existing drugs.

The world's top 50 pharmaceutical companies are currently awaiting FDA approval for about 125 new and supplemental drug applications. About two-thirds of these pending approvals are for new molecular entities (NMEs), new combinations, or new formulations, while the remaining one-third are for new indications.

New drugs

In 2005, the FDA approved only a small number of completely new drugs—only 18 NMEs and 2 therapeutic biologics.[4] This is the third lowest number of approvals in the last 25 years—four more than in 1983, and one more than in 2002. However, 72% of the NMEs approved in 2005 were priority reviews, which is the highest percentage in the agency's history. A noteworthy number of new drug applications in 2005 received either nonapprovable letters or approvable letters with more data required.

In spite of the small number of new drug approvals in 2005, there are over 100 NMEs and therapeutic biologics in the pipeline that could win FDA approval by the end of 2008.[5] This number does not include some additional drug products (new dosage forms or new combination drugs) that may also have an impact on utilization and spending. Across all the drugs in the pipeline, an average of 25 to 30 new NME and therapeutic biologic approvals is possible in each of the next 3 years. This estimate factors in the possibility that approvals for some of the leading pipeline drugs may be delayed until 2009 or beyond, and some may never win approval.

Approximately 370 drugs are currently in Phase III clinical trials for marketing in the United States, and about 700 drugs are currently in Phase II clinical trials.[5] About two-thirds of the products in Phase III development are NMEs. Drugs to treat cancer continue to be the largest area of new drug development, followed by drugs to treat central nervous system (CNS) disorders, diabetes, and cardiovascular disorders.

New indications

Expanding the labeled indications for currently approved drugs continues to be a major focus for product development. Gaining a new indication is a means to expand the market or develop a completely new market for an existing product at a lower cost to the manufacturer than developing a completely new drug. Some of the new uses being pursued by pharmaceutical manufacturers are shown in Table 2. Many of these new indications, if approved, could have a significant impact on utilization growth and spending growth over the next several years.

Table 2. Some new indications pending FDA approval and in Phase II and III clinical trials[5]

Brand name	Generic name	New indication
Actimmune®	interferon gamma-1b	Idiopathic pulmonary fibrosis
Actos®	pioglitazone	Plaque psoriasis
Advair Diskus®	fluticasone/salmeterol	Reducing mortality in patients with COPD
Aricept®	donepezil	Severe Alzheimer's disease
Atacand®	candesartan	Diabetic retinopathy
Avandia®	rosiglitazone	Psoriasis
Avastin®	bevacizumab	Non–small-cell lung cancer; pancreatic cancer; renal cell carcinoma; breast cancer
Avodart®	dutasteride	Reduction of risk of prostate cancer; combination use with alpha-blockers for benign prostatic hypertrophy (BPH)
Diovan®	valsartan	Reduction of risk for progression to type 2 diabetes (combined use with *Starlix®*)
Enbrel®	etanercept	Idiopathic pulmonary fibrosis; Crohn's disease; Wegener's granulomatosis
Erbitux®	cetuximab	Second-line treatment of colon cancer; pancreatic cancer; non–small-cell lung cancer
Evista®	raloxifene	Prevention of breast cancer
Fareston®	toremifene	Reduction of risk for prostate cancer in high-risk patients
Herceptin®	trastuzumab	Early-stage breast cancer following surgery
Humira®	adalimumab	Crohn's disease; juvenile rheumatoid arthritis; ankylosing spondylitis; chronic plaque psoriasis
Kepivance®	palifermin	Oral mucositis associated with chemotherapy for solid tumors
Leukine®	sargramostim	Crohn's disease
Macugen®	pegaptanib	Diabetic macular edema
Namenda®	memantine	Glaucoma; neuropathic pain
Nexavar®	sorafenib	Breast cancer; non–small-cell lung cancer; hepatocellular carcinoma
Prograf®	tacrolimus	Rheumatoid arthritis
Provigil®	modafinil	Fatigue associated with multiple sclerosis
Raptiva®	efalizumab	Psoriatic arthritis
Remicade®	infliximab	Plaque psoriasis
Revlimid®	lenalidomide	Multiple myeloma
Rituxan®	rituximab	Idiopathic thrombocytopenic purpura; maintenance use in nonindolent, non-Hodgkin's lymphoma
Sandostatin LAR®	octreotide	Diabetic retinopathy
Sensipar®	cinacalcet	Secondary hyperparathyroidism in nondialysis patients
Wellbutrin XL®	bupropion extended-release	Seasonal affective disorder
Xifaxan®	rifaximin	Hepatic encephalopathy
Xolair®	omalizumab	Pediatric asthma; perennial allergic rhinitis; peanut and food allergy
Zelnorm®	tegaserod	Gastroesophageal reflux disease (GERD)

Bold text indicates specialty drugs.

New combination products and dosage forms

New combination products, new dosage forms, and new drug-delivery systems continue to be a major focus of product development, and they represent a high percentage of pending new drug applications (NDAs). A good example of a significant new dosage form is *Exubera®*, an inhaled form of regular insulin that is expected to gain widespread use.

The FDA is receiving and approving a record number of NDAs for new dosage forms and combination products. Many of these new products will not provide significant advantages over existing products. Plans should pay particular attention to these new dosage forms, so that savings opportunities created by new first-time generics are not reduced by movement away from generics to new dosage forms that may simply extend the patent life of the base compound.

The continued development of new combination products is a sign that multiple-drug therapy has become a standard management approach. Conditions such as high blood pressure, high cholesterol, diabetes, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, bipolar disorder, and congestive heart failure (CHF) are just a few of the diseases where two or more drugs are being used routinely to achieve optimal disease control. Plans need to consider the overall cost equation associated with these combination drugs and assess whether the combination represents an overall savings opportunity when compared with the use of individual agents.

FIRST-TIME GENERICS

Drugs with total U.S. sales of $30 to $40 billion could lose patent protection over the next 3 years, opening a large potential market for lower-cost generics. Some of these possible patent expirations and first-time generics are shown in Table 3. The number of first-time generics could increase even further if manufacturers continue to launch new generics on an "at risk" basis (prior to patent expiration) or if they secure unexpectedly favorable outcomes in ongoing patent litigation.

The launch of a large number of new, high-volume generics over the next 3 years will help moderate unit-cost growth in several therapeutic categories as utilization shifts to the low-cost generic options. However, new higher-priced drug introductions in the same category may counter some of the savings that would otherwise have been realized. For example, the impact of new generics in the statin class could be partially offset by the introduction of new brand-name products that address both LDL and HDL targets, such as atorvastatin/torcetrapib and simvastatin/niacin/MK524a—possibly in late 2007. Similarly, the introduction of generics for *Effexor®* (venlafaxine) in 2008 could be countered by approval of a new product, desvenlafaxine, in 2007.

Trends in the generics market

An interesting trend in this area is the development of marketing agreements between brand manufacturers and generics manufacturers. These agreements grant generics manufacturers the right to market a generic version of a patented drug a year or more before the scheduled patent expiration, seemingly in exchange for not pursuing patent litigation. By making these agreements, the brand manufacturer can reduce investor concerns that the drug patent may not be upheld in court, which could put revenues from the brand at risk. The generics manufacturers gain the opportunity to market the product earlier than expected—without having to engage in costly patent litigation, where outcomes are uncertain. Four generics manufacturers recently struck an agreement of this type with the manufacturer of *Provigil®* (modafinil), a leading treatment for narcolepsy and shift-work sleep disorder.[8]

Authorized generics are also beginning to change the dynamics of the generics marketplace. These generic products are the same as the brand-name product, but they are marketed under a different label by the brand company or a third-party distributor. Last year the FDA ruled that authorized generics do not have to abide by the 180-day market exclusivity granted by the Hatch-Waxman Act to the first generic on the market. Generics manufacturers have protested this trend; they believe that authorized generics will reduce the number of generics that come to market, leading to less competition and higher prices in the long run.[9]

Table 3. Some potential patent expirations for 2006–2008*
Sources: *Electronic Orange Book*,[6] "*The Pink Sheet*",[7] IMS (retail sales)

Possible patent expiration	Brand name (generic name), manufacturer	Use	2004 U.S. retail sales ($M)
2006	*Zocor*® (simvastatin), Merck	Hyperlipidemia	$3,400
	Zoloft® (sertraline), Pfizer	Depression	$2,700
	Pravachol® (pravastatin), Bristol-Myers Squibb	Hyperlipidemia	$1,600
	Toprol-XL® (metoprolol extended-release), AstraZeneca	Hypertension, CHF	$1,000
	Zofran® (ondansetron), GlaxoSmithKline	Nausea	$706
	Allegra-D® (fexofenadine/pseudoephedrine), Sanofi-Aventis	Allergies	$415
	Ditropan XL® (oxybutynin extended-release), Ortho-McNeil	Overactive bladder	$353
	Activella® (estradiol/norethindrone), Novo Nordisk	Hormone replacement	$53
2007	*Norvasc*® (amlodipine), Pfizer	Hypertension	$2,000
	Ambien® (zolpidem), Sanofi-Aventis	Insomnia	$1,800
	Zyrtec® (cetirizine), *Zyrtec-D 12 Hour*® (cetirizine/pseudoephedrine), Pfizer	Allergies	$1,200
	Imitrex® (sumatriptan), GlaxoSmithKline	Migraine headache	$1,100
	Lotrel® (amlodipine/benazepril), Novartis	High blood pressure	$1,000
	Paxil® *CR* (paroxetine extended-release), GlaxoSmithKline	Depression	$855
	Coreg® (carvedilol), GlaxoSmithKline	Hypertension	$670
	Proscar® (finasteride), Merck	BPH	$240
	Precose® (acarbose), Bayer	Type 2 diabetes	$22
2008	*Advair Diskus*® (salmeterol/fluticasone), GlaxoSmithKline	Asthma, COPD	$2,500
	Risperdal® (risperidone), Janssen	Schizophrenia	$1,600
	Fosamax® (alendronate), Merck	Osteoporosis	$1,500
	Depakote® (divalproex), Abbott	Seizure disorder, bipolar disorder	$670
	Mobic® (meloxicam), Boehringer Ingelheim	Arthritis	$450
	Serevent® (salmeterol), GlaxoSmithKline	Asthma, COPD	$203
	Effexor® (venlafaxine), Wyeth-Ayerst	Depression, anxiety	$110
	Tegretol®*-XR* (carbamazepine extended-release), Novartis	Seizures	$73
	Requip® (ropinirole), GlaxoSmithKline	Parkinson's disease	$72
	Tarka® (trandolapril/verapamil extended-release), Abbott	High blood pressure	$70
	Mavik® (trandolapril), Abbott	High blood pressure	$59
	Kytril® (granisetron), Roche	Chemotherapy-induced nausea/vomiting	$54

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

Biogenerics

Generic versions for a limited number of biotechnology drugs are possible, but biogenerics are not likely to be introduced in the United States until after 2008. Barriers to the market entry of biogenerics are still high, and most, if not all, biotechnology drugs are likely to retain their single-source status for the next 3 years. A primary barrier to market entry is the lack of a federal regulatory framework for approving biogeneric products. Scientific standards still need to be developed to define how bioequivalence or therapeutic equivalence will be evaluated for complex, protein-based biotechnology drugs. The complex molecular structure of these protein-based drugs can be very difficult to characterize, and variations in manufacturing processes can result in changes to the structure of the protein molecules that may impact drug action and immunogenicity.

At this time, it is unclear when a regulatory framework for approval of some biogeneric drugs will become available. The most likely candidates for first-time biogenerics will be less complex proteins that have been available for a long time, such as human insulin, human growth hormone, and erythropoietin.

RX-TO-OTC SWITCHES

The conversion of prescription drugs to OTC status is a trend that is likely to continue. During the next 3 years, the OTC conversion process could extend to additional nonsedating antihistamines (such as *Allegra*® or *Zyrtec*®), weight-loss products (such as *Xenical*®), vaginal antifungals, additional low-potency topical corticosteroids, and perhaps emergency contraceptives. Some of these OTC conversions may be only partial conversions, with both prescription and OTC versions of the products available. Beyond 2009, additional OTC conversions in the proton pump inhibitor (PPI) category are also possible.

KEY THERAPEUTIC DEVELOPMENTS

Over the next 3 years, drug trend will primarily be driven by drugs in five broad therapeutic categories—cardiovascular, CNS, endocrine/diabetes, musculoskeletal/rheumatology, and respiratory. Detailed forecasts of developments in these areas are provided in the following sections of this report.

Future drug trend will also be shaped by developments in the emerging field of pharmacogenomics. Drug treatments will become more personalized, as genetically targeted medications are developed and new diagnostic tests guide drug selection based on genetic variations in individual patients. A review of developments in this new field of medicine begins on page 60 of this report.

Cardiovascular agents

Contribution to plan spending (2005): 24.0%
Contribution to projected trend (2006 to 2008): 33%

TREND PROJECTION

Table 4. Drug trend projection for cardiovascular agents*

Year	2006	2007	2008
Utilization increase	3% to 4%	2% to 3%	3% to 4%
Price and mix increase	5% to 6%	4% to 5%	6% to 7%
Annual total	8% to 10%	6% to 8%	9% to 11%

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

GROWTH DRIVERS

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

- Continued rapid growth in treatment rates for high cholesterol, high blood pressure, coronary artery disease, heart failure, and other cardiovascular conditions
- New drugs for raising HDL cholesterol, new renin inhibitors for lowering blood pressure, and new antiplatelet medications
- First-time generics for two leading statins (*Zocor*® and *Pravachol*®) and a leading antihypertensive (*Norvasc*®)

LIPID-LOWERING DRUGS

Costs for lipid-lowering drugs will continue to grow at a rapid pace—approximately 10% to 15% per year over the next 3 years. The U.S. market for statin and statin combination drugs is currently about $15.5 billion per year[10] and could grow to $20 billion per year over the next few years.

Treatment guidelines

Utilization will continue to grow rapidly, since clinical guidelines have expanded the treatment-eligible population to include patients with normal to mildly elevated cholesterol levels who have risk factors for heart disease.[11] An estimated 36 million people in the United States are candidates for treatment with lipid-lowering drugs, based on national guidelines issued in 2001.[11,12] Recent updates to these guidelines call for more intensive LDL lowering in many patients, which may require the use of combination drug therapy.[13] Clinical studies continue to provide evidence of greater reductions in mortality and morbidity with regimens that lower LDL more aggressively.[14-16]

Statins may also find expanded use in patients with diabetes and heart failure. In January 2004, the American Diabetes Association issued a new recommendation that statins be considered for people with diabetes over age 40.[17] In September 2005, *Lipitor*® was approved for use in adult patients with type 2 diabetes and without clinically evident heart disease to reduce the risk of myocardial infarction (MI) and stroke. Statins have also shown evidence of benefit for patients with nonischemic heart failure.[18] Utilization in these patient populations is likely to increase over the next few years.

Treatment of low HDL cholesterol

Several new drugs that are designed to lower LDL and raise HDL may be approved in 2007 and 2008. These new combination drugs include torcetrapib/atorvastatin and simvastatin/niacin/MK-524A. The success of these new drugs will hinge on the development of strong clinical evidence for the benefits of raising HDL cholesterol. These new brand-name products will contribute to unit-cost growth for lipid-lowering drugs.

First-time generics

New first-time generics for both *Zocor* (simvastatin) and *Pravachol* (pravastatin) will be introduced by mid-2006. These two brand-name drugs currently comprise about one-fourth of the market in the statin class. The new generics will provide an opportunity to moderate unit-cost growth by shifting the product mix toward lower-cost options. However, a careful balance will need to be struck between providing access to higher-potency LDL-lowering statins and statin combinations, when clinically appropriate, while maximizing the opportunities created by these new generics. Single-source statins or statin combination products that can lower LDL more than 50% will still be needed in high-risk patients with intensive LDL-lowering goals and in patients who have markedly elevated LDL levels.

OTC conversions

The FDA is not likely to approve any statin for OTC use in the near term, so there are not likely to be any OTC opportunities in this category during the next few years.

ANTIHYPERTENSIVE DRUGS

Treatment rates

Antihypertensives as a class are the largest single contributor to utilization in the cardiovascular category. Use of these drugs will continue to grow as a larger proportion of people with hypertension are diagnosed and treated. About 50 million Americans have high blood pressure, but only 59% receive treatment for the condition, and more people are expected to develop hypertension as the population ages.[19] According to recent findings from the Framingham Heart Study, individuals between the ages of 55 and 65 have up to a 90% lifetime risk of developing high blood pressure.[20] Increased use of combination drug therapy will also be an important trend driver in this therapeutic class. National guidelines endorse the use of two or more antihypertensives to achieve blood pressure control in many patients.[19]

Treatment of other conditions

The use of antihypertensive drugs could also increase for some patients who do not have hypertension. Recent clinical studies suggest that patients with coronary heart disease, but without hypertension, experience fewer cardiovascular events when taking certain antihypertensive drugs, such as angiotensin II receptor blockers (ARBs) and angiotension-converting enzyme (ACE) inhibitors.[21,22] Utilization of ARBs is likely to continue to grow rapidly as these drugs become more widely used to treat patients following a heart attack and patients with kidney disease or heart failure. Several ARBs, including *Atacand®*, *Diovan®*, and *Cozaar®*, have recently received additional FDA indications for these conditions.

New drugs: Renin inhibitors

The next generation of antihypertensive agents, known as renin inhibitors, will also contribute to growth in this category. One of the drugs in this class, aliskiren, could come to market in early 2007. Unlike the current agents that target angiotensin I (ACE inhibitors) or angiotension II (ARBs), this new agent acts on renin, an enzyme found at an earlier stage in the pathway leading to production of angiotensin II. This new class of agents may prove to be equally effective, and possibly more effective, at lowering blood pressure than either ACE inhibitors or ARBs. Combination use of aliskiren with an ACE inhibitor or an ARB is also being investigated.

First-time generics

The patent expiration for *Norvasc*® (amlodipine besylate), the most widely used dihydropyridine calcium channel blocker, is expected in late 2007. This new generic will offer a significant opportunity to reduce unit costs in this category. A different, non–A-rated salt form of amlodipine may also be introduced around the same time as the A-rated generics for *Norvasc*. The new salt formulation could accelerate price competition among the alternatives to *Norvasc*.

ANTICOAGULANT AND ANTIPLATELET DRUGS

Treatment rates

The use of antiplatelet medications to prevent heart attack, stroke, and other vascular events is expected to continue growing rapidly. The combined use of *Plavix*® and aspirin is becoming more accepted in certain patient populations, such as post-stent patients and high-risk patients with stable coronary artery disease.[23] A combination product containing *Plavix* and aspirin is in the early stages of clinical development for use in patients with peripheral arterial disease and for prevention of thromboembolic events in patients with atrial fibrillation. *Plavix* is also being studied in a large clinical trial for the primary prevention of atherosclerotic events in high-risk patients.

New drugs

New pipeline antiplatelet drugs, prasugrel and AZD6140, with action at the adenosine diphosphate (ADP) receptor similar to *Plavix*, are being studied in combination with aspirin for use in patients with acute coronary syndrome who have undergone percutaneous coronary procedures. These drugs are similar to *Plavix* in their mechanism of action, and both could be introduced a few years before the patent for *Plavix* expires in 2011. Approval of prasugrel may occur by 2008, and AZD6140 could be approved by 2009. These new single-source drugs are likely to increase unit costs in the anticoagulant/antiplatelet category. At this time, however, it is not clear whether either of the new compounds will offer any advantages over *Plavix*.

Several novel oral anticoagulants (Factor 10a inhibitors) are also under clinical development. If approved, these agents are also likely to increase unit costs in this category. Another new drug, ximelagatran, failed to secure approval from the FDA in 2004. This drug had shown great promise as an anticoagulant, but the manufacturer has discontinued development work on the drug.

First-time generics

Although there is a potential threat to the *Plavix* patent from a patent-challenge trial that is slated to start in June 2006, this product is likely to remain single-source until 2011.

ANGINA

Ranolazine (*Ranexa*™), a novel, orally administered partial fatty acid oxidation (pFOX) inhibitor, received FDA approval in January 2006 for the treatment of chronic stable angina. This agent is the first new type of medication to treat angina in over 20 years. Unlike existing angina therapies, ranolazine has a unique mechanism of action that does not rely on changes in heart rate or blood pressure. This new drug will be a second-line agent that is used in combination with calcium channel blockers, beta-blockers, or nitrates, and only after patients have not achieved an adequate response with these other drugs. QTC prolongation with this drug is a concern that will limit its use.

CONGESTIVE HEART FAILURE (CHF)

BiDil®, a fixed-combination product containing hydralazine and isosorbide dinitrate, received FDA approval in June 2005 for the treatment of CHF in self-identified black patients.[24,25] The cost for this brand-name drug greatly exceeds that of the generically available component drugs. However, given the prevalence and seriousness of the condition, and the possible difficulty in matching the recommended dosage of *BiDil* with the individual generically available drugs, this new combination agent may garner significant use in the treatment of CHF among black patients.

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

Year	Generic name	Uses	Potential impact on drug trend
2006	nebivolol	High blood pressure	$
	dronedarone	Arrhythmia	$
2007	aliskiren	High blood pressure	$
	atorvastatin + torcetrapib	High cholesterol/low HDL	$$
	simvastatin/niacin/MK-524A	High cholesterol/low HDL	$$
	azimilide	Arrhythmia	$
	carvedilol extended-release	Heart failure	$
2008	prasugrel	Blood clots, stroke, MI	$
	lercanidipine	High blood pressure	$
	idraparinux	Blood clots	$

$$ = 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 (2005): 22.9%
Contribution to projected trend (2006 to 2008): 18%

TREND PROJECTION

Table 6. Drug trend projection for CNS agents*

Year	2006	2007	2008
Utilization increase	1% to 2%	2% to 3%	2% to 3%
Price and mix increase	4% to 5%	3% to 4%	3% to 4%
Annual total	5% to 7%	5% to 7%	5% to 7%

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

GROWTH DRIVERS

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

- Continued rapid growth in treatment rates for sedative-hypnotics and antiseizure medications
- Slow growth in the use of antidepressants and nonnarcotic analgesics, due to ongoing safety concerns
- New drugs for the treatment of depression, schizophrenia, insomnia, and attention deficit hyperactivity disorder (ADHD)
- First-time generics for two leading antidepressants (*Zoloft*® and *Effexor*) and a leading sedative-hypnotic (*Ambien*®)

SEDATIVE-HYPNOTICS

Treatment of insomnia

Several new insomnia agents came to market during 2005, including *Rozerem*™, *Ambien CR*™, and *Lunesta*™. Although sedative-hypnotic drugs are often used on a long-term basis, they had previously been approved only for shorter-term use. Clinical data for *Lunesta* have demonstrated efficacy for longer-term use (up to 6 months' continuous use) and the product label for *Ambien CR* does not set a limit on duration of use. Marketing of these products for longer-term use could result in increased utilization and costs in this class. Two additional nonbenzodiazepine agents, indiplon and gaboxadol, are also under clinical development, and these drugs may receive FDA approval in 2006 and 2007, respectively.

First-time generics

First-time generics for *Ambien* (zolpidem) are likely to be introduced in 2007. *Ambien* now has about 70% market share in the sedative-hypnotic class, so a first-time generic for this drug could play a major role in moderating unit costs. However, a significant movement to *Ambien CR*, *Lunesta*, or other drugs in this class prior to the *Ambien* patent expiration could reduce the opportunity created by the first-time generics.

SEIZURE MEDICATIONS

Broader indications

Utilization of anticonvulsant drugs continues to grow briskly, due in part to the increased use of these drugs for nonseizure indications and the increased use of combination therapy for refractory seizure disorders. Anticonvulsant agents continue to be studied and used for many nonseizure conditions—such as neuropathic pain, migraine headache prevention, and certain psychiatric disorders. *Lyrica*®, a new drug in this class, was approved in December 2004 for the adjunctive treatment of seizures, postherpetic neuralgia, and diabetic peripheral neuropathy. An additional anticonvulsant drug, rufinamide, may be introduced by 2007.

First-time generics

First-time generics for a widely used antiseizure medication, *Neurontin*® (gabapentin), were introduced in November 2004. These generics will continue to moderate unit-cost growth in the anticonvulsant class over the next few years. However, some of these savings will be offset by higher unit costs for the new brand-name drug *Lyrica*.

ADHD

Treatment trends

Treatment rates for ADHD continue to grow rapidly. Approximately 7.8% of U.S. schoolchildren (ages 4 to 17) have been diagnosed with the disorder, and about 4.3% of children currently receive medication treatment for the condition.[26] Treatment of ADHD in adults is also likely to become a significant driver of utilization growth. One-third to two-thirds of children with the disorder continue to have disabling symptoms as adults, but only 13% of adults with the condition are currently being treated.[27,28] Concerns over the potential cardiovascular risks of stimulant medications—including amphetamine salts and methylphenidate—may moderate utilization growth for both adults and children over the next few years.[29] These safety concerns could shift use in this category to a nonstimulant medication, such as *Strattera*®, or a different type of stimulant medication, such as *Provigil*® (which is not currently indicated for ADHD). Future shifts in therapy mix are difficult to project, since safety risks have been identified for all of the products in this category.

New ADHD medications

Treatment options for ADHD are expanding rapidly. *Adderall XR*® was approved for adult ADHD in August 2004, and *Focalin XR*™ was approved in May 2005 for the treatment of ADHD in adults and children. An NDA for modafinil, under the trade name *Sparlon*™, was filed in December 2004 for ADHD in children, but an approval decision may be deferred until further safety studies can be conducted. Modafinil is currently marketed in a different dosage strength under the brand name *Provigil*. *Daytrana*™, a transdermal patch formulation of methylphenidate, was approved in April 2006 for the treatment of ADHD in children.

ALZHEIMER'S DEMENTIA

Utilization of this class of drugs continues to grow at a rate of about 15% per year. No new drug treatments for Alzheimer's dementia are in the near-term pipeline, so utilization growth will come from increased use of existing drugs in the class for current and expanded indications. *Namenda*®, a new N-methyl-D-aspartate (NMDA) receptor antagonist, received FDA approval late in 2003 for the treatment of severe Alzheimer's dementia. This drug is used alone and in combination with a cholinesterase inhibitor to treat moderate-to-severe Alzheimer's dementia. Despite efforts by the manufacturer, *Namenda* has not received FDA approval for use in mild-to-moderate forms of the disease. An NDA has been submitted for the use of *Aricept*® to treat severe Alzheimer's disease; *Aricept* is currently indicated for mild-to-moderate forms of the disease.

ANTIDEPRESSANTS

Safety concerns

Safety risks associated with antidepressant drugs have contributed to the slow utilization growth in this class over the past year. The FDA now requires that all antidepressants include a black box warning and expanded warning language to alert healthcare providers to an increased risk of suicidality (suicidal thought and behavior) in children and adolescents being treated with these agents.[30,31] The new warning language also advises that adult patients be monitored for signs of clinical worsening and suicidality, but there were insufficient data at the time to justify the same level of warning for adults as for children. The FDA is currently reviewing clinical trial data to determine whether there is evidence of a link between antidepressant use and increased suicidality in adults.[32]

Over the next 3 years, we expect only modest growth in the utilization of antidepressants. The serotonin-norepinephrine reuptake inhibitor (SNRI) class is likely to generate most of the growth, and the utilization of selective serotonin reuptake inhibitors (SSRIs) may continue to decline. New indications for antidepressants, including seasonal affective disorder and neuropathic pain, will contribute to expanded utilization in this class.

New antidepressants

Several new medications are in development for the treatment of depression. *Emsam*® (selegiline transdermal patch) was approved in February 2006, and desvenlafaxine, a follow-on compound for *Effexor* (venlafaxine), could be approved by the end of 2006 or early 2007. Milnacipran, an SNRI agent, may be approved by late 2008 or 2009 for the treatment of fibromyalgia.

First-time generics

Unit-cost growth for antidepressants will be moderated by the availability of new generics and the continuing impact of products that are already available in generic form. Generic versions of *Zoloft* (sertraline) and *Effexor* (venlafaxine) will become available in late 2006 and 2008, respectively.

ANTIPSYCHOTICS

Efficacy and safety concerns

Atypical antipsychotic agents are expected to show only low single-digit utilization growth over the next 3 years. In addition to schizophrenia, many of these medications are also approved for short- and long-term treatment of mania associated with bipolar disorder. Some of these drugs will have warning labels regarding the possible exacerbation or increased risk of new-onset diabetes, although the metabolic side effects appear to be somewhat different for each drug.[33] Results of a large, government-sponsored clinical trial have demonstrated that atypical and traditional antipsychotic agents have comparable efficacy and safety profiles.[34] However, no agent is very good at providing long-term control of schizophrenia. Changing from one drug to another is often necessary.

New antipsychotics

Three new antipsychotic medications—paliperidone, bifeprunox, and asenapine—may be introduced over the next 3 years. However, none of these are likely to be a major advance over existing agents.

NONNARCOTIC PAIN RELIEVERS

Safety concerns

Utilization of nonnarcotic analgesics declined dramatically in 2005 in response to evidence that the COX-2 inhibitors, and all nonsteroidal anti-inflammatory drugs (NSAIDs), are associated with increased cardiovascular risk.[35] Although there are concerns about the cardiovascular safety of traditional NSAIDs, utilization may continue to shift toward these agents, with or without the addition of a PPI for gastric protection. *Mobic*® (meloxicam) showed the largest increase in market share following the withdrawal of *Vioxx*® and *Bextra*®. Generic versions of *Mobic* could become available as early as 2006, but they may not become available until 2008. Use of the remaining COX-2 inhibitor, *Celebrex*®, appears to have stabilized after declining in the first half of 2005. Overall, we expect only moderate utilization growth for the nonnarcotic analgesics over the next 3 years.

New COX-2 inhibitors

The COX-2 drugs in the pipeline, lumiracoxib and etoricoxib, will face more careful review by the FDA because of strong concerns about the cardiovascular risks of drugs in this class. Thus it is not likely that either of these drugs will be introduced before late 2007 or 2008.

NARCOTIC PAIN RELIEVERS

New products

New immediate-release and sustained-release formulations of oxymorphone may be introduced in late 2006 or early 2007. New single-source combination analgesics and new sustained-release products (such as OROS hydromorphone) are also anticipated over the next 3 years. These new brand-name products will help drive higher unit costs for narcotic analgesics.

First-time generics

Unit costs have been moderated by the recent introduction of generic versions of *OxyContin*® (oxycodone) extended-release tablets and *Duragesic*® (fentanyl) patches. However, a federal appeals court has recently determined that the *OxyContin* patent may be enforceable.[36] Further litigation over the *OxyContin* patent will determine whether the generic versions of this product can continue to be sold.

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

Year	Generic name	Uses	Potential impact on drug trend
2006	indiplon immediate-release and controlled-release	Insomnia	$
	ropinirole controlled-release	Restless legs syndrome	$
	rasagiline	Parkinson's disease	$
	rotigotine	Parkinson's disease	$
	paliperidone	Schizophrenia	$
	natalizumab	Multiple sclerosis	$
	L-lysine-d-amphetamine	ADHD	$
	armodafinil	Narcolepsy	$
	selegiline orally disintegrating tablet	Parkinson's disease	$
	dextromethorphan + quinidine	Emotional expression disorder	$

continued on next page

Table 7. Some ambulatory-use CNS agents in the pipeline *(continued)*

2007	oxymorphone immediate-release and sustained-release	Pain	$
	rufinamide	Seizure disorder	$
	lamotrigine controlled-release	Bipolar disorder, schizophrenia	$
	gaboxadol	Insomnia	$
	sumatriptan + naproxen	Migraine headache	$
	galantamine extended-release	Alzheimer's disease	$
	bifeprunox	Schizophrenia	$
	zolpidem orally disintegrating tablet	Insomnia	$
	desvenlafaxine	Depression	$
	hydromorphone extended-release	Pain	$
2008	asenapine	Schizophrenia	$
	neramexane	Alzheimer's disease	$
	lumiracoxib	Rheumatoid arthritis, osteoarthritis, pain	$
	etoricoxib	Rheumatoid arthritis, osteoarthritis, pain	$
	quetiapine sustained-release	Schizophrenia	$
	teriflunomide	Multiple sclerosis	$
	milnacipran	Fibromyalgia	$$
	SPD 503	ADHD	$

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

Endocrine and diabetes agents

Contribution to plan spending (2005): 7.4%
Contribution to projected trend (2006 to 2008): 13%

TREND PROJECTION

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

Year	2006	2007	2008
Utilization increase	3% to 4%	3% to 4%	4% to 5%
Price and mix increase	7% to 8%	8% to 9%	8% to 9%
Annual total	10% to 12%	11% to 13%	12% to 14%

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

GROWTH DRIVERS

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

- Rapid utilization growth due to increased prevalence and more aggressive treatment of diabetes
- Increased use of multiple drugs and combination drugs to treat diabetes and its complications
- A wide array of new products—oral agents, inhaled insulin products, and injectables

DIABETES

Obesity and diabetes

The prevalence of diabetes has increased steadily over the past 20 years, and it has been accelerated by the epidemic of obesity in the United States.[37-39] During the past year alone, 1.5 million new cases of diabetes were diagnosed in adults.[40] The prevalence of diabetes in children is also increasing rapidly.[39,40] The rising prevalence of diabetes will contribute to steady utilization growth for diabetes medications over the next few years. The prevalence of obesity and overweight in the United States has accelerated the development of diabetes in both adults and children. During the period 1999 to 2002, about 65% of adults between the ages of 20 and 74 were overweight, including 31% who were obese.[41] Based on similar criteria, about 30% of children and adolescents between the ages of 6 and 19 are overweight, including 15% who are obese.[42]

Tighter control

A long-term clinical trial has recently demonstrated that tight control of blood glucose can reduce the macrovascular, as well as the microvascular, complications of diabetes.[43] 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.[44] Two- and three-drug combinations are frequently needed to help achieve adequate blood glucose control.

Only about 7% of patients with diabetes achieve their target goals for blood glucose, cholesterol, and blood pressure.[45] The remaining patients represent an undertreated population that may drive future utilization growth for diabetes medications, including oral hypoglycemic agents, insulin products, and drugs that help manage the complications of diabetes.

Inhaled insulin

The first inhaled insulin product, *Exubera*, received FDA approval in January 2006. One or two additional inhaled insulin products may come to market in the next few years. In patients with type 2 diabetes, inhaled insulin will generally be used in combination with oral agents to achieve more tightly controlled postprandial blood glucose. Some concerns about potential long-term pulmonary toxicity associated with *Exubera* remain unanswered. However, the changes in pulmonary function that have been reported with this product appear to be small and reversible. For nonsmoking patients who do not have a history of asthma or other respiratory conditions, this safety consideration is unlikely to significantly limit the acceptance of inhaled insulin products.

New injectables

Two new injectable treatments 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, it slows gastric emptying to delay entry of ingested sugar into the bloodstream, and it inhibits secretion of glucagon. Over time, the use of *Byetta* may lead to weight loss—an atypical side effect among the drugs used to treat diabetes. This new injectable is likely to have a significant impact on utilization and cost in the diabetes category. Concerns about the potential hypoglycemic effects of *Symlin* appear to have limited its utilization to date. These injectable agents are likely to be used in combination with existing therapies, which will accelerate utilization growth for diabetes medications.

A third injectable agent, liraglutide, is currently in development and may be introduced in 2008. Liraglutide acts similarly to exenatide, but is administered only once daily. A once-weekly dosage form of exenatide is also in clinical development and could reach the market by 2008.

New oral agents

Ruboxistaurin, a protein kinase C inhibitor, is in development for the treatment of diabetes complications, including diabetic retinopathy, diabetic macular edema, and diabetic peripheral neuropathy. In Phase III trials, this drug has demonstrated a significant reduction in sustained moderate vision loss in patients with diabetic retinopathy. Ruboxistaurin will be an

add-on treatment to existing therapies for diabetes. It is likely to be a significant contributor to utilization growth in the category, given the prevalence of retinopathy in patients with diabetes.

Several new oral drugs in the dipeptidyl peptidase IV inhibitor class are in Phase III development, including vildagliptin, sitagliptin, and saxagliptin. These drugs increase the amount of glucagon-like peptide-1 in the blood by inhibiting its metabolizing enzyme. They may provide a benefit similar to that of *Byetta*, while acting through a completely different mechanism. These agents appear to be well-tolerated without significant gastrointestinal side effects. They are also likely to be weight-neutral or associated with weight loss, and they are not associated with hypoglycemia. These drugs will be used as part of multiple-drug combination treatment for patients with diabetes.

Glitazones

Current glitazone products, such as *Actos*® and *Avandia*®, are likely to see continued market share growth, since they are often used in combination therapy for type 2 diabetes. This will increase unit costs for the category, since these single-source brands are significantly more expensive than generic products. Current patent challenges on *Avandia* could allow generics as early as 2008. However, several patents on *Avandia* extend to 2015, so the outcome of these patent challenges remains uncertain. It is unlikely that *Actos* will lose patent protection by the end of 2008.

Muraglitazar (*Pargluva*™), the latest glitazone to be recommended for approval by the FDA Advisory Board, will likely never reach the market due to unexplained findings of increased mortality in the clinical trial data. Two other glitazones, tesaglitazar and TAK-654, are still on track for FDA approval in the next few years. It is unclear whether these new agents offer any advantages over existing drugs in this class. Like the injectable agents described above, these new glitazones will be used in combination therapy to achieve better glucose control.

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

Year	Generic name	Uses	Potential impact on drug trend
2006	rosiglitazone + metformin extended-release	Type 2 diabetes	$
	sitagliptin	Type 2 diabetes	$
2007	tesaglitazar	Type 2 diabetes	$
	ruboxistaurin	Diabetic retinopathy	$$
	vildagliptin	Type 2 diabetes	$
2008	liraglutide	Type 2 diabetes	$
	valsartan + nateglinide	Reduction in risk for new-onset type 2 diabetes	$$
	pulmonary insulin (inhaled)—second formulation	Types 1 and 2 diabetes	$
	saxagliptin	Type 2 diabetes	$
	idursulfase	Hunter's syndrome	$
	alglucosidase alfa	Pompe's disease	$
	sulodexide	Diabetic nephropathy	$$
	exenatide long-acting formulation	Type 2 diabetes	$
	TAK-654	Type 2 diabetes	$

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

Musculoskeletal and rheumatological agents

Contribution to plan spending (2005): 5.0%
Contribution to projected trend (2006 to 2008): 8%

TREND PROJECTION

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

Year	2006	2007	2008
Utilization increase	1% to 2%	1% to 2%	1% to 2%
Price and mix increase	11% to 12%	11% to 12%	9% to 10%
Annual total	12% to 14%	12% to 14%	10% to 12%

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

GROWTH DRIVERS

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

- Increased use of high-cost biologics as first-line treatments for rheumatoid arthritis
- Increased use of biologics to treat psoriasis, psoriatic arthritis, ankylosing spondylitis, and other new indications
- New specialty drugs for the treatment of osteoporosis and rheumatoid arthritis
- First-time generics for a leading osteoporosis treatment (*Fosamax*®)

OSTEOPOROSIS

Treatment trends

Utilization of osteoporosis drugs grew more slowly in 2005 than in prior years, and only moderate growth is expected over the next 3 years. Once-weekly bisphosphonates, such as *Fosamax* and *Actonel*®, account for most of the utilization in this category. A new once-monthly formulation of *Boniva*® (ibandronate; approved in March 2005) is beginning to make inroads in this market. *Miacalcin*® (calcitonin) and *Forteo*® (parathyroid hormone) are also used to treat osteoporosis, but they account for a very small share of utilization. Many people with osteoporosis are not yet being treated, so increased detection and treatment rates may drive some utilization growth over the next few years.[46]

New specialty drugs for osteoporosis

A new recombinant parathyroid hormone product, *Preos*®, is likely to be introduced in 2006. This agent will compete with *Forteo*, which is currently reserved for patients who cannot or should not use other osteoporosis treatments. It is not clear whether the new product will have any advantages over *Forteo*, or whether it will also require class labeling regarding an increased risk of osteosarcoma. In general, parathyroid hormone is used only in patients who are at high risk for bone fracture or who fail to tolerate or respond to bisphosphonates.

Another new medication, denosumab, affects bone growth through a novel mechanism of action—inhibiting the receptor activator of NF-kappa B (RANK) pathway. The RANK pathway mediates the activity of osteoclasts, the cells that are responsible for breaking down bone. Denosumab is a monoclonal antibody that inhibits the RANK pathway and therefore reduces osteoclast activity. Preliminary data suggest that this drug may be more effective than *Fosamax* in building bone. Denosumab is an injectable drug that is administered by a healthcare professional once every 6 months. The drug could receive FDA approval by late 2007 or early 2008.

In January 2006, a new intravenous formulation of *Boniva* was approved for use every 3 months for the treatment of osteoporosis. *Zometa®*, an injectable bisphosphonate, is being studied for a new indication as a once-yearly treatment for the prevention of osteoporosis.

First-time generics

Based on a recent court ruling, generic versions of *Fosamax* (alendronate) will reach the market as early as 2008. A first-time generic for this drug could have a very favorable impact on unit costs for the osteoporosis category.

RHEUMATOID ARTHRITIS

Treatment trends

Although tumor necrosis factor (TNF) inhibiting drugs, such as *Enbrel®* and *Humira®*, comprise only a small fraction of utilization in the musculoskeletal and rheumatology category, these agents are responsible for almost half of the total costs. These new biologics are being adopted more frequently for early use in rheumatoid arthritis treatment, as results from clinical trials continue to demonstrate the excellent efficacy and safety profiles of these drugs.[47] Also, the early use of combination therapy (such as methotrexate with either *Enbrel* or *Humira*) appears to help slow disease progression more than either drug alone and is gaining support in the medical community.[47]

New indications for leading biologics

Recent FDA-approved indications for *Enbrel*, such as plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis, represent significant new markets for this drug. *Enbrel* is also in clinical trials for the treatment of idiopathic pulmonary fibrosis, a rare but severe illness that currently has few treatment options. *Humira* received FDA approval for the treatment of psoriatic arthritis in 2005, and it is being studied for the treatment of psoriasis, Crohn's disease, and ankylosing spondylitis. FDA approval of these indications could significantly drive up utilization of these biologics.

New specialty drugs

Orencia® (abatacept), a new biologic for rheumatoid arthritis, was approved by the FDA in December 2005. *Orencia* is a once-monthly, intravenously administered drug that interferes with a costimulatory signal that causes T-cell activation and proliferation. This drug has also been shown to be effective in patients who fail to respond to TNF inhibitors.

Several new drugs targeting T-cell and B-cell activity are in the near-term pipeline for rheumatoid arthritis. Certolizumab pegol, a once-monthly, subcutaneously administered, pegylated anti-TNF antibody, with actions similar to *Enbrel* and *Humira*, could receive FDA approval by 2007. *Rituxan®*, a drug that interferes with B-cell activity and is currently approved for non-Hodgkin's lymphoma, was approved in February 2006 for the treatment of patients with rheumatoid arthritis who fail to respond to TNF inhibitors.

Tocilizumab, a novel anti-interleukin-6-receptor monoclonal antibody, is in clinical development for rheumatoid arthritis and could be introduced in late 2007 or 2008. This intravenously administered drug has shown some impressive results in Phase III trials. It may also find uses for Crohn's disease and Castleman's disease.

Introduction of these new drugs will increase the utilization of biologic agents for the treatment of rheumatoid arthritis. Rapid unit-cost growth is likely to continue for the foreseeable future, as additional biologic agents enter the market and as new indications, such as the use of *Enbrel* for psoriasis, foster use of higher dosing regimens.

GOUT

The NDA for febuxostat, a potential replacement drug for allopurinol, was submitted to the FDA in December 2004. Allopurinol, a xanthine oxidase inhibitor, is a widely used drug that has been available as a generic product for many years. The newer agent would be the first new oral treatment for gout to be introduced in 40 years. Although it appears to be superior to allopurinol in lowering the high serum uric acid levels that contribute to gout attacks, clinical studies have not shown a greater decrease in gout attacks with febuxostat compared with allopurinol. Nonetheless, this new brand-name drug may quickly replace allopurinol for the prevention of gout attacks, which could significantly increase the unit costs of drug treatments for gout.

Table 11. Some ambulatory-use arthritis and osteoporosis drugs in the pipeline

Year	Generic name	Uses	Potential impact on drug trend
2006	febuxostat	Gout	$$
	recombinant parathyroid hormone	Osteoporosis	$
2007	bazedoxifene	Osteoporosis	$
	certolizumab pegol	Crohn's disease	$
	lasofoxifene	Osteoporosis	$
2008	**denosumab**	Osteoporosis	$
	zoledronic acid	Osteoporosis, Paget's disease, bone metastasis in breast cancer	$
	tocilizumab	Rheumatoid arthritis	$
	abetimus	Lupus erythematosus	$$

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

Respiratory agents

Contribution to plan spending (2005): 8.8%
Contribution to projected trend (2006 to 2008): 7%

TREND PROJECTION

Table 12. Drug trend projection for respiratory agents*

Year	2006	2007	2008
Utilization increase	1% to 2%	1% to 2%	1% to 2%
Price and mix increase	6% to 7%	5% to 6%	5% to 6%
Annual total	7% to 9%	6% to 8%	6% to 8%

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

GROWTH DRIVERS

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

- Increased emphasis on inhaled corticosteroids as first-line asthma controllers due to safety concerns about the use of long-acting beta-agonists
- New inhaled and oral treatments for pulmonary arterial hypertension
- Additional first-time generics for nonsedating antihistamines (including *Zyrtec*)
- First-time generics for a leading nasal corticosteroid (*Flonase*®)

ASTHMA AND COPD

Treatment trends

The use of long-acting bronchodilators, such as *Serevent*® (salmeterol), is likely to decline in response to concerns about an increased risk of mortality associated with these drugs.[48,49] 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.[48] However, these considerations are not likely to produce a significant slowdown in the use of *Advair Diskus*® (a combination of salmeterol and fluticasone). The therapy mix for inhaled asthma controllers has shifted towards *Advair* over the past few years, and this trend is likely to continue. *Advair* is also indicated for the treatment of COPD associated with chronic bronchitis, and it is being studied for a new indication—the reduction of mortality in patients with COPD.

New asthma controllers

A new inhaled corticosteroid, *Asmanex*® *Twisthaler*® (mometasone), was approved in March 2005. Additional single-agent and combination inhalers are in clinical development, and a ciclesonide inhaler (*Alvesco*®) is currently pending approval. These new products will contribute to unit-cost growth for asthma controller medications over the next 3 years.

New treatments for COPD

Spiriva® (tiotropium) is emerging as the primary inhaled anticholinergic drug for COPD treatment—replacing *Atrovent*® (ipratropium), which is available in generic form. This shift in therapy mix will continue to increase unit costs in the respiratory category. It appears unlikely that any of the pipeline PDE-4 inhibitor treatments for COPD (such as roflumilast) will be introduced by the end of 2008.

New indications for a specialty drug

Xolair®, a monoclonal antibody indicated for allergic asthma, is progressing slowly through clinical trials for the treatment of allergic rhinitis and food allergies, including peanut allergy. Utilization of this drug under the pharmacy benefit has been relatively low since the product was approved in June 2003. Utilization could increase significantly if *Xolair* is demonstrated to be effective for peanut allergy, a condition that affects approximately 2 million people in the United States.[50]

First-time generics

No asthma controller medications are expected to become available in generic form during the next 3 years. Some products have gained extended exclusivity with the conversion from chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA) propellants. The current lack of bioequivalence standards for inhaled corticosteroids is also an impediment to broader availability of generics.

PULMONARY ARTERIAL HYPERTENSION (PAH)

New treatments

Pulmonary arterial hypertension continues to be an area for significant new drug development. *Ventavis®* (inhaled iloprost) was approved for the treatment of PAH in December 2004. This new prostacyclin is available in a dosage form that is less invasive than other prostacyclin drugs, which need to be administered intravenously or subcutaneously. *Revatio®* (sildenafil; approved in June 2005) is a promising new treatment option for PAH that offers a benign side effect profile. Two new endothelin A receptor antagonists, sitaxsentan and ambrisentan, are under development for the treatment of PAH; these new products are likely to be introduced in 2006 and 2007, respectively.

Treatment trends

In the past, the drugs used to treat PAH were parenterally administered medications, 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 cost impact of treatment is likely to fall more under the pharmacy benefit. Over the next several years, additional clinical data demonstrating the benefit of combination therapy with these agents could become available.

ALLERGIC RHINITIS

OTC conversions

Nasal corticosteroids to treat allergic rhinitis may be a target for a partial OTC conversion, since the FDA has already determined that allergic rhinitis is suitable for self-treatment. If a nasal corticosteroid is eventually approved for OTC use, it may be for a slightly different indication or strength than the prescription-only version. Thus, both OTC and prescription products could be available.

First-time generics

First-time generics for *Allegra* (fexofenadine) became available in 2005 and generics for *Allegra-D®* may be introduced by the end of 2006. Generics for *Zyrtec®* (cetirizine) and *Zyrtec-D 12-Hour®* are likely to become available in 2007. Availability of these generic products will significantly reduce unit costs in the nonsedating antihistamine class.

A first-time generic for *Flonase* (fluticasone) was approved in February 2006 under a new guidance developed by the FDA for evaluating bioequivalence in nasal corticosteroid products. Market availability of generic fluticasone began in March 2006.

Table 13. Some ambulatory-use respiratory agents in the pipeline

Year	Generic name	Uses	Potential impact on drug trend
2006	aformoterol inhaler	Asthma	$
	ciclesonide inhaler	Asthma	$
	sitaxsentan	Pulmonary arterial hypertension	$
	budesonide + formoterol	Asthma and COPD	$
2007	**ambrisentan**	Pulmonary arterial hypertension	$
	mometasone + formoterol	Asthma and COPD	$
	olopatadine nasal spray	Allergic rhinitis	$
2008	**treprostinil inhalation**	Pulmonary arterial hypertension	$
	indacaterol	Asthma and COPD	$
	loteprednol nasal	Allergic rhinitis	$

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

Other therapeutic agents

Pipeline developments in other therapeutic categories could also have a significant impact on drug trend over the next 3 years (Table 14). These include new drug treatments for gastrointestinal conditions, cancer, and age-related macular degeneration.

GASTROENTEROLOGY

Ulcer and heartburn

No new drugs or first-time generics are expected in this therapeutic category over the next 3 years. Spending growth for PPIs is likely to be moderate (in the low single-digit range), driven mostly by price increases among the brands.

Chronic constipation

In January 2006, *Amitiza*™ (lubiprostone) was approved for the treatment of chronic constipation, a disorder that affects millions of Americans. *Amitiza* and *Zelnorm*® are the only two FDA-approved drugs for the treatment of chronic constipation; they are likely to generate moderate utilization growth in the gastroenterology category.

Inflammatory bowel disease

New indications for biologic agents used in the treatment of inflammatory bowel disease, which affects over 1 million people in the United States, will contribute to increased utilization over the next 3 years. In September 2005, *Remicade*® was approved for a significant new indication, the treatment of moderate-to-severe ulcerative colitis. Additional biologic agents for the treatment of Crohn's disease will also contribute to rising utilization over the next few years. *Humira* and a new drug, certolizumab pegol, are currently in Phase III clinical development for Crohn's disease. The costs of these drugs may appear in different therapeutic categories, depending on the first FDA-approved indication for the drug and the primary chapter assignment of the drug involved.

ONCOLOGY

Treatment trends

Drugs for the treatment of cancer are the largest area for new drug development, with hundreds of new cancer drugs and new indications for existing cancer drugs in clinical development. From a treatment standpoint, cancer is becoming a more chronic condition. Many of the newer and more targeted drugs are better tolerated, and they are often administered for months or years until there is disease progression. Unlike drugs of the past, which were so toxic that they could only be used for a few cycles, many of the newer drugs are used as a form of maintenance treatment. Treatment costs will continue to expand as these drugs are used on a longer-term basis, and in combination regimens that can cost $5,000 to $10,000 for a month of treatment.

Many new cancer drugs are incremental to current treatments, so they may be significant drivers of new utilization. Careful monitoring and management of cancer treatment costs will be essential. Specialty pharmacy distribution of these drugs can provide an effective solution for managing costs by limiting experimental uses and driving larger and more consistent discounts.

New oral drugs

Orally administered cancer drugs will be increasingly important trend drivers over the next few years, given the large number of new drugs in the pipeline and the likelihood of expanded indications and off-label usage for existing drugs. Many of these drugs are likely to be more expensive than current treatments, and many will be used in addition to current treatments. Recently approved and potential products include:

- *Nexavar*® (sorafenib) was approved in December 2005 for the treatment of advanced renal cancer, and *Sutent*® (sunitinib) was approved in January 2006 for advanced renal cancer and gastrointestinal stromal tumors. Each drug costs in the range of $4,000 to $6,000 per month.
- *Revlimid*® (lenalidomide) received approval in December 2005 for reducing transfusion requirements in patients with myelodysplastic syndrome. The primary impact of this drug on trend is likely to be in the treatment of multiple myeloma; the FDA has recently granted a priority review for this indication.
- Orally administered cancer drugs in development include dasatinib, vatalanib, atrasentan, and satraplatin. Dasatinib, an oral tyrosine kinase inhibitor, is likely to be approved in 2006 for the treatment of chronic myelogenous leukemia that is refractory to *Gleevec*®.

Supportive treatments

Supportive care therapies—such as *Epogen*® (epoetin alfa), *Aranesp*® (darbepoetin alfa), *Neupogen*® (filgrastim), and *Neulasta*® (pegfilgrastim)—represent a significant share of the medication costs for cancer treatment, and they are a significant driver of trend. Utilization of these agents to treat chemotherapy-induced anemia and neutropenia is expected to grow rapidly over the next 3 years. A continuing shift from *Neupogen* to *Neulasta* is likely to increase unit costs for chemotherapy-induced neutropenia treatment. The NDA for continuous erythropoietin receptor activator (CERA) was submitted in December 2005. This drug may be introduced by late 2006 for the treatment of anemia in patients with chronic renal failure.

OPHTHALMOLOGY

Macular degeneration

A major area for drug development continues to be the treatment of age-related macular degeneration (AMD), a condition that affects millions of older Americans. Several drugs are in development for the "wet" form of this disease, which is a leading cause of blindness in the elderly. Ranibizumab is designated for priority review by the FDA and may be approved for the treatment of AMD in mid to late 2006. Like *Macugen*®, which was approved in December 2004, ranibizumab is an injectable antivascular endothelial growth factor (anti-VEGF) agent. Phase III trial data for ranibizumab suggest that it may initially improve visual acuity, in addition to delaying the loss of visual acuity. Anecortave, an antiangiogenic steroid compound, may be approved for AMD treatment in 2007. Like *Macugen*, this drug is administered by injection into the eye, although the injection technique is different. Finally, rostaporfin, which is similar to the currently marketed *Visudyne*®, may be introduced in 2006 for use with laser phototherapy.

These new treatments for AMD will dramatically increase utilization and costs for ophthalmological drugs. However, based on current payment patterns, most of these costs are likely to be billed under medical benefits rather than pharmacy benefits. These drugs will have a significant impact on the Medicare drug budget, given the prevalence of AMD and the relatively high costs for these therapies. However, these costs are likely to be borne primarily by Medicare Part B, rather than Medicare Part D.

Table 14. Other therapeutic categories: Some ambulatory-use drugs in the pipeline

Year	Generic name	Uses	Potential impact on drug trend
2006	**Anti-infectives**		
	telbivudine	Hepatitis B	$
	anidulafungin	Systemic fungal infections	$
	TMC-114	HIV infection	$
	posaconazole	Fungal infections	$
	Antineoplastics		
	decitabine	Myelodysplastic syndrome	$
	dasatinib	Chronic myelogenous leukemia (CML) refractory to *Gleevec*®	$
	genasense	Refractory chronic lymphocytic leukemia (CLL)	$
	Gastrointestinal agents		
	alvimopan	Postsurgical ileus	$
	Ophthalmology		
	travoprost + timolol	Glaucoma	$
	rostaporfin	Age-related macular degeneration	$
	ranibizumab	Age-related macular degeneration	$$
	Other		
	varenicline	Smoking cessation	$
	rimonabant	Weight loss	$$
	naltrexone long-acting formulation	Alcoholism	$

continued on next page

Table 14. Other therapeutic categories: Some ambulatory-use drugs in the pipeline *(continued)*

2007	**Anti-infectives**		
	garenoxacin	Bacterial infections	$
	faropenem	Sinusitis, community-acquired pneumonia	$
	dalbavancin	Gram-positive infections	$
	viramidine	Hepatitis C	$
	maraviroc	HIV infection	$
	Antineoplastics		
	panitumumab	Metastatic colon cancer	$
	satraplatin	Prostate cancer	$
	efaproxyn	Brain cancers	$
	Gastrointestinal agents		
	certolizumab pegol	Crohn's disease	$
	Ophthalmology		
	latanoprost + timolol	Glaucoma	$
	anecortave	Age-related macular degeneration	$
	brimonidine + timolol	Glaucoma	$
	Other		
	continuous erythropoietin receptor activator	Anemia in chronic kidney disease	$
	tetrabenazine	Huntington's disease	$
2008	**Antineoplastics**		
	sipuleucel-T	Prostate cancer	$
	vandetanib	Thyroid cancer	$
	atrasentan	Prostate cancer	$
	rubitecan	Pancreatic cancer	$
	MDX-010	Malignant melanoma	$
	vatalanib	Colorectal cancer	$$
	canfosfamide	Non–small-cell lung cancer	$
	epratuzumab	Non-Hodgkin's lymphoma	$
	lapatinib	Solid tumors	$$
	Gastrointestinal agents		
	renzapride	Irritable bowel syndrome	$
	Genitourinary agents		
	trospium extended-release	Overactive bladder	$
	topical alprostadil	Erectile dysfunction, female sexual dysfunction	$
	fesoterodine	Overactive bladder	$
	dapoxetine	Premature ejaculation	$$
	sapropterin	Phenylketonuria	$
	s-oxybutynin	Overactive bladder	$
	Other		
	miraxion	Huntington's disease	$
	eltrombopag	Thrombocytopenia	$
	eculizumab	Paroxysmal nocturnal hemoglobinuria	$
	testosterone transdermal patch	Female hypoactive sexual desire disorder	$$
	motavizumab	RSV infection	$
	asoprisnil	Uterine fibroids	$

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

Personalizing medicines: Genetic testing and the future of care

Imagine being able to walk into your doctor's office and present a "smart card" encoded either with the sequence of your genome itself or with an access code granting permission to log on to a secure database containing your genomic information. Armed with a complete and accurate understanding of your unique genome, your physician would be able to prescribe the right drug in the right dosage at the right time to effectively treat your condition, with little or no concern that the therapy won't work or that you will suffer adverse side effects.[51]

Medications are currently designed to be used by a broad population, yet each person's response to a medication is unique. In a typical population, there can be as much as a 20- to 30-fold variation in the range of physiological responses to medications—some people may have significant adverse events while others may have no therapeutic response to the same drug administered at the same dose.[52] The wide variability in response can be linked to a variety of factors, including our individual genetic makeup. Since 2003, when the mapping of the human genome was completed, the importance of our genetic structure and its relationship to medication therapy has become better understood.

In practice, the potential variability in patients' responses to drugs may have little effect on a clinician's decision. For many medications, there is no significant compromise of efficacy or safety that results from selecting a medication and dosing regimen using population-based rather than patient-specific criteria. In some cases, however, failure to accurately predict an individual's response can lead to therapeutic failure or unpredictable—even fatal—side effects. In these situations, physicians currently manage the patient through close clinical assessment or frequent laboratory monitoring. This empiric approach works well in many circumstances, but many of these issues could be avoided by adopting a more personalized approach to the clinical development and therapeutic use of medications through advances in *pharmacogenomics*.

Pharmacogenomics examines the inherited variations in genes that influence an individual's response to medications. It explores how these variations can be used to predict the therapeutic or adverse responses a patient may have to a medication. This new field of research has a large potential impact on clinical practice, because it can help clinicians determine which drugs and dosages will work best for an individual patient. It will also help shape the development of new medicines that are targeted to the genetic makeup of specific groups of patients. Many experts in the field believe that pharmacogenomics holds the key to successfully developing and safely using medications.

Back to basics: A genetics primer

The total genetic information of any organism is called its *genome*. This genetic information is contained in the double-stranded structure of the deoxyribonucleic acid (DNA) molecule. Only four different chemical structures (known as nucleotides) make up this long, complicated DNA molecule. These four base nucleotides are always arranged in pairs. The sequence of these four "base pairs" in the DNA molecule helps define the structure and function of the organism.

The human genome consists of long, coiled, double-stranded chains (called "helixes") containing about 3 billion base pairs. Coded within this double-stranded helix is the information for 20,000 to 25,000 different genes.[52] These genes contain the complete set of instructions that every living cell needs to survive. However, these genes comprise only about 1% to 3% of the total length of the entire human genome.[52] The rest of the genome consists of areas that separate these genes and regions that regulate them.

THE HUMAN GENOME

About 99.9% of the human genome is thought to be identical in all human beings.[52] The remaining 0.1%, however, is what determines our genetic individuality. It contributes to the underlying development and expression of a variety of genetically linked diseases. It is also one of the factors that determine an individual's response to medications, making it particularly interesting to those involved in pharmacogenomics research.

Genes and variations

Identifying alterations in the normal sequence of base pairs within human DNA is the starting point for understanding how genetic variability impacts the response to medications. The most abundant and simple alteration in the DNA sequence is known as a *single-nucleotide polymorphism* (SNP). An SNP involves replacing one of the four nucleotides in the normal base pair sequence with one of the other three—a single replacement in a DNA strand billions of base pairs long.

Some of these genetic variations are benign, but some can have a dramatic effect on the body's structure or function. If the SNP occurs in a region that defines a gene, or in a region that controls or regulates a gene, then a new version of the gene can be created (a new *genotype*). The new genotype may contribute to differences in an individual's physical appearance or physiological functioning (their *phenotype*). Finding a consistent correlation between specific SNPs, new genotypes, and the resulting physical or functional variation is essential to any clinical application of genetics.

Variations in drug response

About 10 million SNPs have been identified and localized in the human genome.[52] Not all of these have been linked to detectable phenotypic differences. Multiple SNPs affecting the same gene may be required to create a new phenotype. The genetic changes that shape individual differences in drug response may be even more complex—they may involve variations on several different genes that affect drug metabolism, drug transport, and drug targets. There are still major challenges ahead in matching disease susceptibility and variations in drug response to specific SNPs or patterns of SNPs (haplotypes) within the genome.

Microarray chips—preparations containing synthetic pieces of DNA arranged on a rigid surface—can currently detect up to 100,000 different SNPs.[52] These chips can identify genetic variations that affect many specific drug responses. Unfortunately, the exact number of SNPs required to obtain a complete genetic profile remains unknown. While it would be helpful to test individuals only once in their lifetime and create a comprehensive drug response profile, this is still far from being a reality.

GENETIC TESTING: CURRENT APPLICATIONS

In several therapeutic areas, pharmacogenomics already provides information and testing tools that can be used in clinical decision-making. Three types of tests are currently available to help identify genetic variations that affect a person's response to medications:

1. Tests for variations in drug-metabolizing enzymes
2. Tests for variations in drug membrane transporters
3. Tests for variations in drug receptors

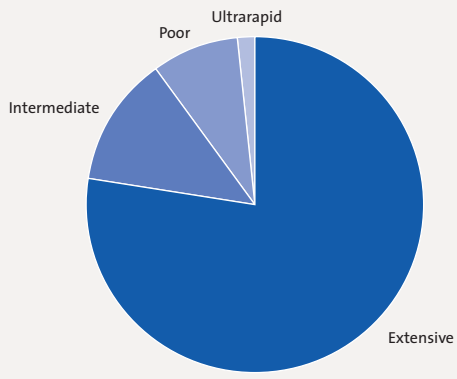
These tests all measure some type of *biomarker*—a biochemical indicator that can identify a structural or functional difference that is based on genetic variations. Some biomarker tests directly measure genetic polymorphisms (SNPs), and some measure proteins or other molecular structures that help identify individuals with a particular genetic variation.

1. Drug metabolizers

Genetic testing can be used to identify genetic variations that determine the levels and activity of common drug-metabolizing enzymes. This testing is particularly useful for the cytochrome P450 liver enzymes, which are responsible for the activation or inactivation of many medications. Three enzymes in this group (CYP2D6, CYP2C19, and CYP2C9) are particularly important, because they metabolize about 40% of currently available medications.[53] These three enzymes also exhibit a significant degree of genetic polymorphism, which results in several different phenotypes.

The CYP2D6 enzyme is responsible for metabolizing about 25% of currently available medications—including many antidepressants, antipsychotic agents, antiarrhythmics, beta-blockers, and cancer drugs.[54] For many drugs, this enzyme is the primary pathway for inactivating (eliminating) the drug. For other drugs (such as codeine), its activity is responsible for converting the drug into its biologically active form. The gene encoding for the CYP2D6 enzyme has more than 80 different polymorphic forms, which result in four distinct phenotypes: slow metabolizers, intermediate metabolizers, extensive metabolizers, and ultrarapid metabolizers (Figure 3).[55,56]

Figure 3. Population differences in drug metabolism by CYP2D6 enzymes



Phenotype	Prevalence	Characteristic drug response*
Poor metabolizer (PM)	7% to 10%	Drugs are metabolized very slowly, so they may accumulate to toxic levels. At standard dosages, the risk of side effects may be higher than for extensive metabolizers.
Intermediate metabolizer (IM)	10% to 15%	Diminished capacity to metabolize drugs. Lower-than-average dosages may be sufficient to achieve therapeutic response.
Extensive metabolizer (EM)	73% to 82%	Typical ("normal") rate of drug metabolism.
Ultrarapid metabolizer (UM)	1% to 2%	Unusually high rate of drug metabolism. Drugs may not reach therapeutic levels, so they may be ineffective at standard dosages.

Note: Prevalence is the estimated rate in Caucasian populations.[56]

*Characteristic drug responses apply to drugs that are primarily inactivated (eliminated) by the activity of CYP2D6 enzymes.

Gene-based microarray tests are now available to detect the genetic polymorphisms for several metabolic enzymes. These tests can help identify patients who have the genetic predisposition for one of the four metabolizer phenotypes, making it possible to identify those who may exhibit a slow, intermediate, normal, or very rapid metabolism rate for certain medications. This information could be used to select medications or dosing regimens based upon the patient's phenotype. For example, patients who are slow metabolizers may be at increased risk for adverse side effects from a drug, while the same dosage may be benign and ineffective for patients who are ultrarapid metabolizers.

As of 2004, the product labels for about 13 FDA-approved drugs contained information about the possible impact of a patient's drug-metabolizing enzyme phenotype on drug response, and only seven of these drugs indicated that this information might be useful to guide therapy.[52] Examples of currently approved medications with enzyme phenotype information in their product labels are shown in Table 15.

Table 15. Product labels that specify an impact of enzyme phenotype on drug action[52,57]

Drug	Drug use	Drug-metabolizing enzyme	Enzyme family
Abilify® (aripiprazole) *Strattera*® (atomoxetine) *Provigil*® (modafinil) *Mellaril*® (thioridazine) *Enablex*® (darifenacin)	Schizophrenia ADHD Narcolepsy Schizophrenia Urinary incontinence	CYP2D6	Cytochrome P450
Celebrex® (celecoxib)	Arthritis	CYP2C9	Cytochrome P450
Vfend® (voriconazole)	Fungal infections	CYP2C19	Cytochrome P450
theophylline	Asthma	CYP1A2	Cytochrome P450
Purinethol® (mercaptopurine) *Imuran*® (azathioprine)	Cancer and immunological disorders	Thiopurine methyl transferase (TPMT)	Thiol methylating enzymes
Camptosar® (irinotecan)	Colorectal cancer	Uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1)	Conjugating enzymes
Aczone™ (dapsone) gel	Acne	Glucose-6 phosphate dehydrogenase	Oxidative enzymes

Although genetic tests are currently available, testing for a patient's metabolizer status is not yet a routine part of clinical practice. Genetic testing is not likely to become routine until it has been demonstrated to improve outcomes when compared with the current practice of empiric monitoring.

Two medications—mercaptopurine and azathioprine—provide a good example of the challenges involved in using metabolizer status in clinical practice. These medications are used for the treatment of Crohn's disease, systemic lupus erythematosus, and various cancers (such as leukemia). Since these medications can be very toxic, blood counts are monitored every 1 to 2 weeks to look for serious myelosuppression (reduction in blood cells). These two medications are primarily inactivated by a liver enzyme, thiopurine S-methyl transferase (TPMT), which metabolizes them to less toxic substances. Due to a genetic alteration, about 1 in 300 people do not produce the TPMT enzyme. These people should be treated with only 5% to 10% of the normal dose of these drugs in order to avoid serious side effects.[52]

Genetic tests are now available to prospectively identify individuals who are missing the TPMT enzyme. Despite the inclusion of TPMT genotyping in the prescribing information for mercaptopurine, the use of this type of genetic testing is still limited. The test is not routinely performed, even though the phenotype that leads to drug toxicity can be reliably identified by genetic testing. The reasons for this disparity may include the low prevalence of the altered genotype (1 in 300), the perceived high cost of testing 300 patients to detect the one requiring a dosage reduction, and the lack of clear proof that this testing provides better care than routine blood count monitoring.

2. Drug transporters

A second type of genetic testing measures genes that affect the activity of drug membrane transporters (substances that help drugs move across membranes in and out of cells). For example, the MDR1 gene encodes for p-glycoprotein, a transporter that is involved in moving several types of drugs across cell membranes, including anticancer drugs and protease inhibitors used in the treatment of HIV. Genetic alterations in the MDR1 gene change the amount of drug transporter and appear to reduce the efficacy of protease inhibitors.[52] Although tests for these genetic variations are available, their effectiveness in clinical practice has not been conclusively demonstrated. Further research is needed to determine whether MDR1 genetic testing can produce better clinical outcomes than adjusting dosages based on viral load.

3. Drug receptors

A third important focus for biomarker testing is to identify variations in drug receptors. Genotypic variations in these receptors can affect how an individual responds to a drug. For example, a polymorphism in the genes that code for the beta-adrenergic receptor can reduce a patient's response to inhaled beta-agonist bronchodilators (such as albuterol).

The impact of genetic variations in drug receptors is not as well understood as the variations in drug-metabolizing enzymes. However, some tests of receptor genotypes and phenotypes are already available, and these tests can help identify patients who will respond to a specific drug therapy. Tests for biomarkers can be conducted on the patient or on a tissue sample (such as a biopsy sample from a tumor). Table 16 provides examples of some currently available drugs for which receptor-specific biomarker tests are available. Biomarkers for drug receptor activity can help predict how effective a drug will be in a given patient.

Table 16. Product labels that identify a potential role for receptor phenotype in drug therapy[52]

Drug	Use	Biomarker	Comment
Erbitux® (cetuximab) *Tarceva*® (erlotinib) *Iressa*® (gefitinib)	Colorectal cancer Lung cancer Lung cancer	Epidermal growth factor receptor (EGFR) expression	Presence of biomarker may influence response, but more data are needed
Herceptin® (trastuzumab)	Breast cancer	Overexpression of tumor growth factor receptor, HER2	Drug is indicated for patients overexpressing this biomarker
Gleevec® (imatinib)	Chronic myelogenous leukemia, gastrointestinal stromal tumors	Philadelphia chromosome, CD117 (c-kit) positive	Drug is most useful in patients with this biomarker

Testing of biomarkers for receptor activity has been particularly useful in the oncology field:

- Breast cancer tissue can be tested for expression of HER2/neu, a tumor growth factor receptor protein, which determines the response to *Herceptin*®.
- Gastrointestinal stromal tumors can be analyzed for the c-kit receptor protein to help predict a patient's response to *Gleevec*.
- Tests for epidermal growth factor receptor (EGFR) may help predict the response to certain anticancer drugs (such as *Erbitux*®, *Tarceva*®, *Iressa*®, and panitumumab), since lack of EGFR expression may reduce the response to these drugs.

Changing clinical practice

Several tests of genotypic variations in drug response are already available, but the impact on the day-to-day practice of medicine is still relatively small. Several reasons may help account for this:

- The need for education on how and when to use the information
- The difficulty and expense of performing tests and assays
- The lack of demonstrated cost-effectiveness in comparison to traditional empiric monitoring
- The rarity of a single-gene cause for drug response variability
- Uncertainty about the predictive value of genetic tests to accurately identify patients
- Ethical, legal, and social considerations

These barriers need to be addressed before genetic testing can become a widely used and accepted part of the clinical decision-making process.

GENETICS IN DRUG DEVELOPMENT

Product labeling

Routine adoption of genetic tests in clinical practice will depend on how effectively the tests predict drug response and how effectively the knowledge is communicated to clinicians. The FDA has taken steps to address both of these needs. In 2005, the FDA issued a guidance for the pharmaceutical industry on the submission of information about genetic variability and its effects on drug response.[58] The standards for proving that a test is a good predictor of drug response are very high; large studies and compelling statistics will probably be needed to demonstrate that a specific test can be a useful predictive tool.

The FDA is also working to increase the amount of useful pharmacogenetic information that is placed in drug product labels. To warrant inclusion in the product labels, the evidence for a test's reliability and validity will need to meet the agency's standards. In most cases, manufacturers are not yet in a position to supply this level of supporting evidence, since few genetic tests have been fully validated as predictors of drug responders or adverse events.

Drugs in the pipeline

Over the past few years, manufacturers have begun to incorporate pharmacogenetic considerations into their drug development process and their communications to healthcare professionals. During 2004 and 2005, five new drug products included genetic or other biomarker information that might be relevant to the use of the medication. These products represented about 10% of the 49 NMEs approved by the FDA during that time period.

Over the next 5 to 10 years, about 10% to 20% of drugs in development are likely to be associated with genetic tests to help identify the patient populations likely to respond to treatment.[52] Cancer drugs are currently one of the biggest areas of new drug development, so genetic testing is likely to become an integral feature of therapy management for cancer patients.

During the next 3 years, several new drugs are likely to be introduced with genetic or other biomarker information included in the product label (Table 17). The protocols for each of these drugs may incorporate some sort of genetic testing that determines how they should be used.

Table 17. Pipeline drugs that may be associated with genetic or other biomarker testing

Drug	Use	Possible test	Comment
idursulfase	Mucopolysaccharidosis II	Genetic testing for abnormality at Xq27-q28	Chromosomal testing to help diagnose disease
paliperidone	Schizophrenia	Metabolizer status of CYP2D6	Action of drug may be affected by poor or ultrarapid metabolizer status
desvenlafaxine	Depression	Metabolizer status of CYP2D6	Action of drug may be affected by poor or ultrarapid metabolizer status
indacaterol	Asthma/COPD	Genetic testing for polymorphism at beta-adrenergic receptors	Polymorphism at beta-adrenergic receptors may affect drug action
panitumumab	Colorectal cancer	Testing for EGFR receptors	Response may be linked to EGFR expression
dasatinib	Chronic myelogenous leukemia	Testing for Philadelphia chromosome	Response may be better in Philadelphia chromosome–positive patients
vatalanib	Colorectal cancer	Metabolizer status of CYP2D6	Action of drug may be affected by poor or ultrarapid metabolizer status

PERSONALIZING HEALTHCARE

While there is still a long way to go before developments in pharmacogenomics become a significant part of everyday practice, they have already changed the way some diseases are treated. Over time, more information will become available about the correlations between specific genotypic variations, the related phenotypes, and how these can be tested or targeted to refine treatment regimens.

Advances in technology will make it possible to create a microarray containing enough SNPs to provide a "once in a lifetime" genetic profile for an individual. In order to effectively and efficiently utilize all of this new genetic information in clinical practice, information technology resources will have to be developed that can catalogue and organize this vast quantity of information into usable databases. Profiles from these databases could be used to assist physicians in selecting the best drug and dosage based on the individual's genetic makeup.

A comprehensive genetic profile could also help identify individuals who are at increased risk of developing specific diseases before they develop signs or symptoms. Interventions for these at-risk individuals could delay or even prevent disease development or progression. For example, scientists have isolated a genetic mutation that is associated with a 40% increase in the risk of developing type 2 diabetes if a person carries one copy of the gene, and a 140% increase in risk when two copies are present.[59] This discovery could lead to the development of a simple genetic test to identify people who are at increased risk for diabetes. These individuals could be appropriately monitored and treated before serious complications of the disease occur. Given the devastating consequences and costs associated with diabetes, the cost savings from this genetic test could be enormous.

Tailoring medication therapy to account for individual differences at the genetic level can help make medications safer and more effective. As often happens, the science is a step ahead of the technology required to incorporate these advances into the clinical practice of medicine, but the science and the technology are both advancing rapidly. Just as 15-minute "rapid strep" tests for sore throats made routine 48-hour throat cultures unnecessary, pharmacogenetic testing may supplement or replace many of the medication monitoring and testing procedures in current use.

PROFILING PLAN DESIGN:

THE GENETICS OF CHANGE

3

The power of a plan is in its genome.

This section will help you:

- **Evaluate your pharmacy benefit in comparison with your peers.**
  When assessing your current benefit, an analysis of what your peers are doing is a good place to start. What strategies do other plans use for managing cost and utilization, and how does your benefit design compare with theirs?

- **Dig deeper into your benefit management philosophy.**
  Changes in plan design are ultimately shaped by your unique approach to benefit management. To identify opportunities for change, it is helpful to focus on the four key factors that define your benefit philosophy—your **PBM DNA**™.

Peer comparisons

Different groups of plan sponsors—including employers, health plans, and state and local governments—often have different ways of achieving their benefit management goals. This is often due to differences in their member populations, financial considerations, or regulatory constraints. Peer comparisons among groups offer a logical starting point for reviewing benefit offerings, because they can show how plan sponsors with similar characteristics structure their prescription benefit plans. The following sections review some common benefit management strategies and their prevalence within different groups of plan sponsors.*

The strategies reviewed here are grouped into five basic categories:

- Cost management
- Generic incentive programs
- Mail-order incentive programs
- Clinical management
- Management of specialty drugs

*Peer comparisons are based on plan design data for client groups with active membership in Medco's book of business in 2005. Clients were divided into peer groups—employer, government, labor, health plan, and third-party administrator—according to their underlying business model.

Cost management strategies

A key to benefit management is determining what level of cost the plan is willing to absorb and what percentage it will ask its members to contribute. As prescription drug costs rise, many plan sponsors have to choose between increasing their contribution or sharing at least part of the cost increases with their members. Cost sharing can be accomplished in a number of different ways, including raising premiums or increasing co-payments.

The cost share borne by members is highly variable from plan to plan, ranging from 0% for some plans to as high as 40% for others. Most plans cover 75% to 80% of benefit costs, and members are responsible for the remaining 20% to 25%.

CO-PAYMENTS AND COINSURANCE

A common cost-sharing strategy in prescription benefit plans is to require a co-payment or coinsurance payment on each prescription that a member purchases.

Co-payments are flat-dollar amounts paid at the point of purchase. Co-payments make costs more predictable for members, but plans may need to update the co-payment amounts periodically to ensure that the member contribution to the benefit remains consistent. When setting co-payment levels, plan sponsors must consider their objectives for member cost-share, their overall tolerance for member dissatisfaction, and the potential impact of higher cost-share on medication adherence. Co-payments typically charged by Medco clients are summarized in Table 1; the amounts vary by plan design, formulary tier, and dispensing channel (retail vs. mail).

Coinsurance payments are a percentage of the plan's total cost for the prescription. Coinsurance allows plans to keep up with drug cost increases without introducing plan changes, but it can also lead to greater variability in prescription costs for members. For plans that use coinsurance, the typical levels are summarized in Table 2; the levels vary by plan design, tier, and channel.

Table 1. Typical fixed-dollar co-payments in tiered plan designs

Plan design	Median co-payment (range)	
	Retail	Mail
Two tier	Tier 1: $10 ($5 to $10) Tier 2: $16 ($10 to $20)	Tier 1: $15 ($10 to $20) Tier 2: $30 ($15 to $40)
Three tier	Tier 1: $10 ($10 to $10) Tier 2: $25 ($20 to $30) Tier 3: $40 ($30 to $50)	Tier 1: $20 ($15 to $25) Tier 2: $50 ($30 to $62) Tier 3: $80 ($50 to $100)

Note: The table shows the median and interquartile range (25th to 75th percentiles) for member co-payments in client plans that use fixed-dollar co-payments.
In a two-tier design, tier 1 is typically applied to generic drugs and tier 2 is applied to brand drugs.
In a three-tier incentive design, tier 1 is typically applied to generic drugs, tier 2 is applied to preferred brand drugs, and tier 3 is applied to nonpreferred brand drugs.
In a three-tier open design, tier 1 is typically applied to generic drugs, tier 2 is applied to single-source brand drugs, and tier 3 is applied to multisource brand drugs.

Table 2. Typical coinsurance rates in tiered plan designs

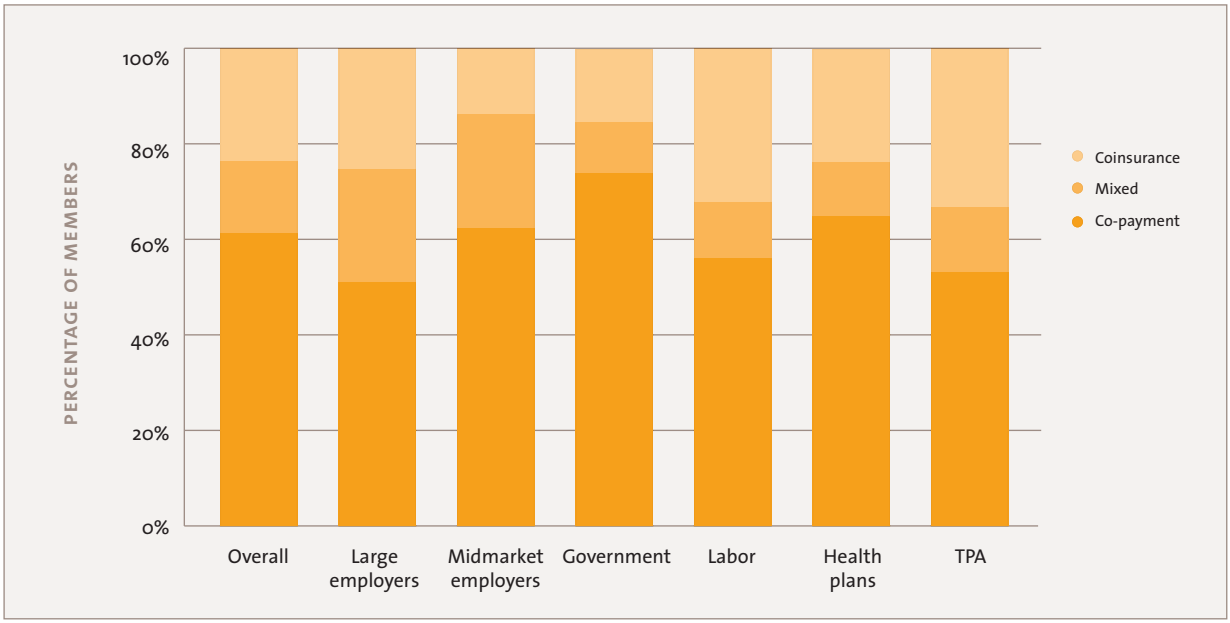
Plan design	Median coinsurance rate (range)	
	Retail	Mail
Two tier	Tier 1: 20% (20% to 30%) Tier 2: 30% (20% to 50%)	Tier 1: 20% (20% to 25%) Tier 2: 25% (20% to 50%)
Three tier	Tier 1: 20% (15% to 25%) Tier 2: 25% (20% to 30%) Tier 3: 40% (30% to 50%)	Tier 1: 20% (20% to 25%) Tier 2: 25% (20% to 30%) Tier 3: 45% (30% to 50%)

Note: The table shows the median and interquartile range (25th to 75th percentiles) for member coinsurance in client plans that use coinsurance.

Analysis:

- The majority of plan sponsors (61%) use flat-dollar co-payments in their plan design. The remainder use coinsurance (24%) or a mixed design that combines co-payments and coinsurance in different tiers of the formulary (15%). (See Figure 1.)
- Co-payment plan designs are least prevalent among large employers, since many of these plans have moved to coinsurance or mixed co-payment/coinsurance designs.
- The use of coinsurance is most prevalent in labor plans and third-party administrator (TPA) plans.

Figure 1. Plan designs with co-payment, coinsurance, or mixed cost-share structures
Source: Medco data



Note: For each client group, the figure shows the percentage of members who participate in a plan using co-payments, coinsurance, or mixed co-payment/coinsurance structures. Data shown are for 2005.
Large employers: Employers with ≥15,000 members
Midmarket employers: Employers with <15,000 members
TPA: Third-party administrator

Plan considerations:

- Some plans include an *out-of-pocket maximum* that caps the amount that members contribute toward their benefits. This can be defined as an annual maximum, a per-prescription maximum, or both. Both types of out-of-pocket maximums are designed to be set high enough that most members will not reach them, but low enough to protect members from catastrophic expenses. Per-prescription maximums can help remove some of the unpredictability associated with coinsurance by setting a clear upper limit on what members will pay.
- Some plans include a *benefit maximum* that caps the amount the plan sponsor will cover. The benefit maximum can be defined as an annual limit, a per-prescription limit, or both. These benefit caps can limit plan sponsors' financial exposure, but they may also have a significant impact on plan members. Some members may not be able to afford their medications, and they may discontinue therapy if their medications become too expensive.

FORMULARY STRUCTURE AND INCENTIVES

Formularies define the set of medications that are preferred by the plan. The design of a formulary is a key tool for managing costs in a prescription benefit plan. There are three primary types of formulary—incentive, open, and closed.

Incentive formularies often use three or more tiers to provide financial incentives for patients and their physicians to select lower-cost drugs that are preferred by the plan. For example, in a typical three-tier structure, the lowest member payments are charged for generic drugs (first tier), higher payments are charged for preferred brand-name drugs (second tier), and the highest payments are charged for nonpreferred brands (third tier). The member payments could be either fixed-dollar co-payments or coinsurance (with or without caps). Some plans now use a mixed co-payment/coinsurance structure, which typically features a fixed co-payment for drugs in the lowest tier and coinsurance for medications in higher tiers.

Open formularies provide equal coverage for brand-name drugs in the therapeutic categories that are included in the benefit, regardless of their formulary status. An open formulary may be a single tier with a co-payment or coinsurance rate that applies to all covered prescriptions. It may also be structured into tiers to provide some financial incentive for generic drug use. For example, in a typical three-tier open formulary, the lowest tier is for generic drugs, the middle tier is for single-source brand-name drugs, and the highest tier is for multisource drugs (brand-name drugs for which lower-cost generic equivalents are available). This incentive structure is designed to avoid having members pay at the highest level for single-source medications, for which no generic equivalents are available.

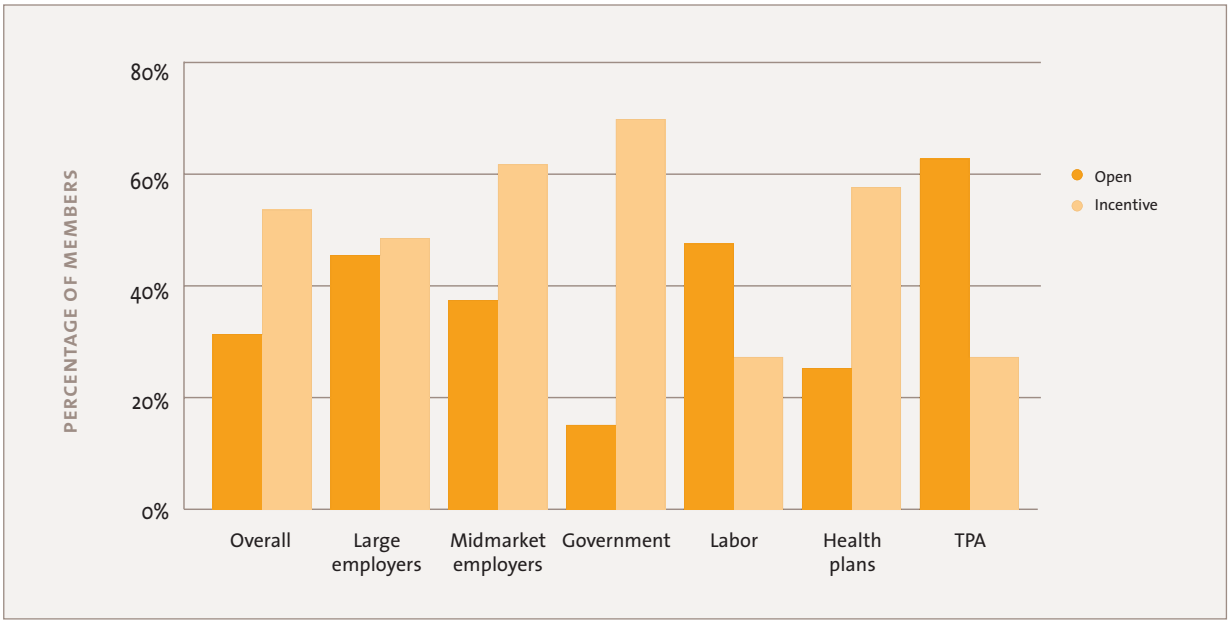
Closed formularies only provide coverage for the plan-preferred drugs in the therapeutic categories that are included in the benefit. They provide a strong financial incentive for members and physicians to choose drugs preferred by the plan, because only the preferred drugs are covered by the plan. Members have to pay the full retail price if they purchase a drug that is outside the formulary. Plans with closed formularies often have an appeals process to address special circumstances where formulary drugs cannot be used.

The types of formulary designs implemented by Medco clients are summarized in Figure 2 (open and incentive formularies) and Figure 3 (number of tiers). Closed formularies and four-tier designs are not included, because these are relatively uncommon.

Analysis:

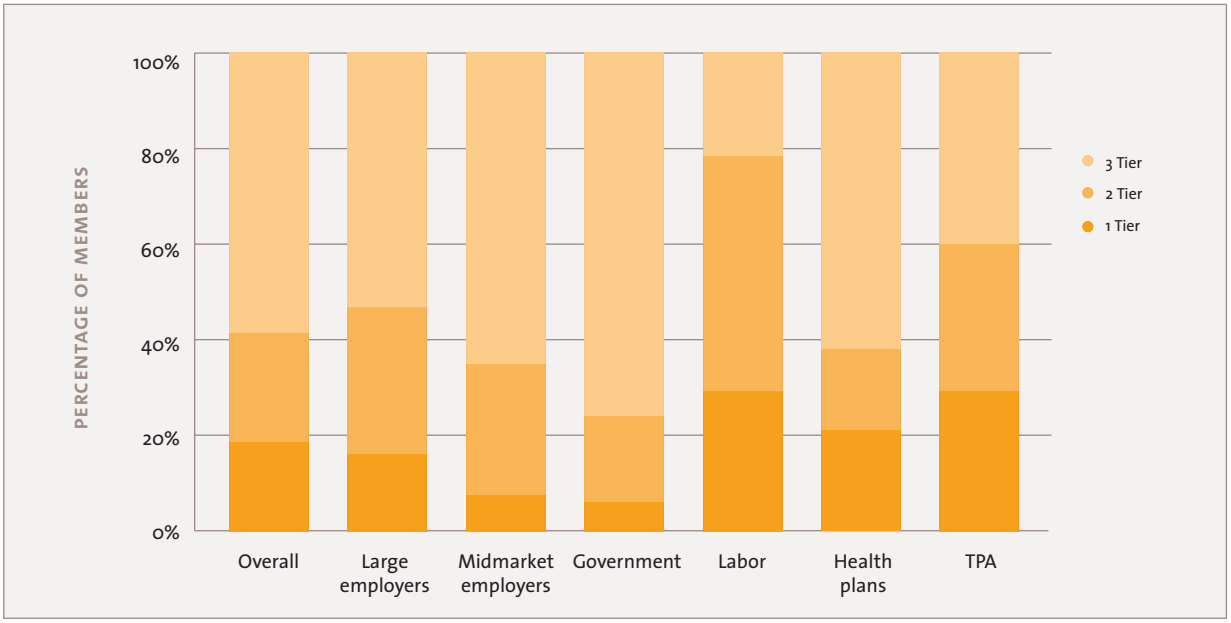
- Labor plans and TPAs are the only client groups for which open formularies are more common than incentive formularies.
- Almost 70% of members in government plans use incentive formularies.
- Three-tier incentive formularies are now the most popular among Medco clients.

Figure 2. Plan designs with open or incentive formularies
Source: Medco data



Note: For each client group, the figure shows the percentage of members who participate in a plan with an open formulary design or an incentive formulary design. Data shown are for 2005.

Figure 3. Plan designs with one-tier, two-tier, and three-tier formularies
Source: Medco data



Note: For each client group, the figure shows the percentage of members who participate in a plan using a one-tier, two-tier, or three-tier formulary. Data shown are for 2005. Plans with other formulary designs (including four-tier formularies) are excluded from the analysis.

Plan considerations:

- Open formularies offer greater member choice, but they result in lower manufacturer rebates for plan sponsors.
- Closed formularies offer less member choice but greater potential for plan savings. These formularies are sometimes structured in tiers to provide more targeted financial incentives. The typical structure is two-tiered, with generics in the first tier and covered brands in the second tier.
- A very restrictive incentive formulary may require as much as 100% member coinsurance for certain nonpreferred medications; the member would pay 100% of the plan's negotiated discount price for these nonpreferred drugs. However, this is still better than a closed formulary, where members pay 100% of the *retail* price for all nonformulary drugs.

Case study: Adding a fourth tier

A technology company with a large union workforce added a fourth co-payment tier to its incentive formulary in 2005. A key goal of the new design was to manage costs by encouraging members to use lower-cost brand-name drugs. The plan sponsor accomplished this by splitting what was previously the second tier—preferred brand-name drugs—into two separate tiers: low-cost preferred brand drugs and high-cost preferred brand drugs. The co-payments for retail and mail-order prescriptions were as follows:

	2004 (prior plan)	2005 (new plan)
Retail	$8/**25**/30	$10/**25/35**/40
Mail order	$16/**50**/60	$20/**50/70**/80

Results:

- The new four-tier design helped the plan achieve a significant reduction in trend—from 16.3% in 2004 to 1.7% in 2005. Member cost-share increased about 2.7%, mainly due to the co-payment increases in the new first, third, and fourth tiers.
- The plan's formulary compliance (use of the first and middle tiers) increased to more than 92% in 2005. The new co-payment structure increased the differential between preferred and nonpreferred drugs, encouraging members to investigate generic and preferred brand alternatives.
- By creating greater member awareness of the cost differential between brand-name drugs and generics, the new design encouraged greater use of generic drugs. The generic dispensing rate increased by 3.5% from 2004 to 2005.

DEDUCTIBLES

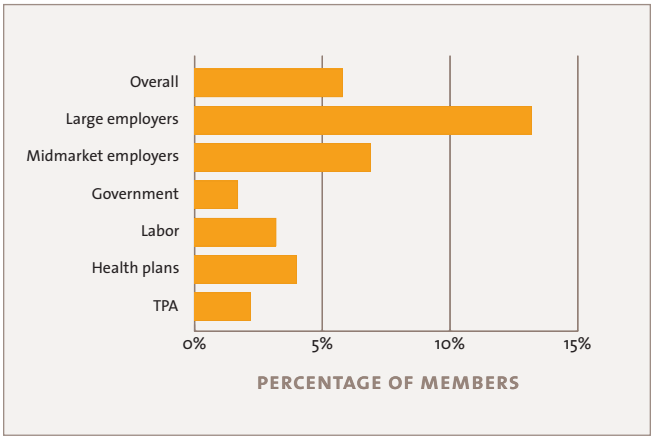
Some plan designs offer coverage for prescription drugs only after a deductible has been met, similar to how car insurance typically works. Deductibles are a staple of consumer-driven health plans (CDHPs); these plans often combine high-deductible coverage with a healthcare account that can be used for a member's initial medical and pharmacy expenses. A deductible is also included in the basic Medicare Part D drug benefit, which requires the first $250 in drug expenses to be paid by the enrollee.

Beyond CDHPs and the new Medicare benefit, few prescription drug plans currently include deductibles. However, the widespread use of deductibles in plans based on Medicare Part D may spur some plan sponsors to reevaluate their position.

Analysis:

- Only 6% of members are currently enrolled in prescription benefit plans with deductibles (see Figure 4).
- Employer groups make the most extensive use of deductibles in their prescription plans. The use of deductibles is lowest in government plans.

Figure 4. Plan designs that include deductibles
Source: Medco data



Note: For each client group, the figure shows the percentage of members who participate in a prescription benefit plan that includes a deductible. Data shown are for 2005.

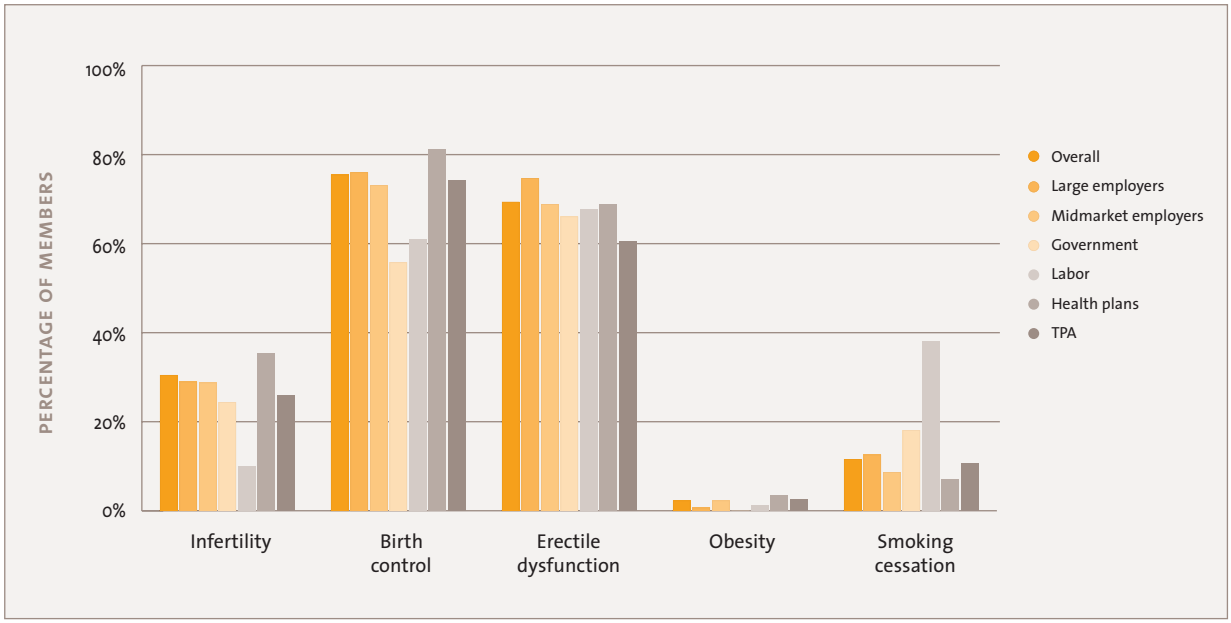
Plan considerations:

- Although the number of groups implementing deductibles is currently low, the number is likely to increase as more clients offer CDHPs and as enrollment in Medicare-sponsored prescription drug plans increases.
- Some plan sponsors may opt to waive the deductible for generic drugs, but they may require that the deductible be met prior to covering brand-name medications for which generic alternatives are available.
- Many members are already familiar with how deductibles work (from their medical, dental, or car insurance), so the addition of a deductible to their prescription benefit is not likely to be a significant source of confusion.
- Because of the increasingly sophisticated administration of prescription claims, it is becoming easier for plan sponsors to incorporate deductibles into their plan designs.

COVERAGE EXCLUSIONS

Plan sponsors can also manage costs by excluding specific drugs or drug categories from coverage under the benefit plan. Standard exclusions include drugs that are used exclusively for cosmetic or experimental purposes; OTC drugs are also generally excluded. Plans may also consider excluding specific therapeutic categories from coverage under the benefit. These categories may include weight-loss drugs, fertility drugs, oral contraceptives, drugs for erectile dysfunction, or smoking cessation products.

Figure 5. Plans that include coverage for specified conditions
Source: Medco data



Note: For each client group, the figure shows the percentage of members who participate in a prescription benefit plan that provides coverage for the indicated condition. Data shown are for 2005.

Analysis:

- The pattern of coverage exclusions by therapeutic category is similar across client groups (see Figure 5). Birth control agents and drugs for erectile dysfunction are covered by the majority of plans, but prescription weight-loss treatments are commonly excluded.
- Only 12% of members participate in plans that provide coverage for smoking cessation agents, and 31% of members are in plans that provide coverage for infertility treatments.

Plan considerations:

- Excluding coverage for certain types of medications can result in savings to plans. However, plan sponsors need to weigh many factors when determining coverage exclusions—including the organization's benefit philosophy, financial resources, and member demographics. One consideration is whether the plan will focus primarily on treating illnesses, or whether (and to what degree) it will also provide coverage for drugs that enhance health, function, and appearance.
- Plan sponsors should also consider inclusion or exclusion questions in the context of the organization's medical plan (such as coverage for infertility) to ensure alignment of the coverage offered through the medical and pharmacy benefits.
- Some plans allow members to obtain excluded drugs at the plan's discounted rate. This offers members the added security of having their prescription reviewed through the plan's health and safety checks.
- Prior authorization rules can be established to allow coverage under defined conditions for a drug that is normally excluded. Plans can also offer clinical review and appeals procedures for certain categories of excluded drugs.

Trend to watch: Consumer-driven health plans (CDHPs)

Traditional cost-sharing strategies—such as tiered formularies and coinsurance—have already helped members become more aware of the full cost of the prescription healthcare they receive. CDHPs take the next step—they give members more access to cost information and they broaden the incentives to control costs. CDHPs often include a fixed contribution from the plan sponsor and a high deductible that members must meet before coinsurance or other coverage begins.

Medco has been managing the prescription benefit portion of CDHPs for more than 7 years, and it currently serves about 40% of the total CDHP market. Although only about 50 Medco clients currently offer CDHPs, the market for these plans is growing rapidly. Market growth has been fueled by the federal government's promotion of health savings accounts.

For plan sponsors, a key to success is the recognition that CDHPs are not just a plan design change. Members will need more sophisticated information and support systems to help them understand and manage their healthcare costs. The pharmacy benefit is one important area of healthcare spending where members can be actively involved in managing their costs. As a pharmacy benefit manager, Medco offers multiple tools and services to help members research their medication options, understand the cost implications before they fill a prescription, and track their purchases over time.

Generic incentive programs

One of the primary forces behind the declining drug trend in recent years has been the increased use of generic drugs. The average generic dispensing rate for Medco clients increased to 51.5% in 2005, the first year for which more generics were dispensed than brand-name drugs. Benefit plan sponsors can promote generic drug use by providing tiered incentives, co-payment waivers, or other financial incentives for their members.

TIERED INCENTIVES

Tiered formularies are a commonly used tool for encouraging members to use generic drugs as an alternative to brand-name drugs. This is achieved by setting lower co-payment or coinsurance levels for generic drugs, which are generally assigned to the first tier of the formulary. Typical spreads between tiers in multiple-tier formularies are shown in Tables 1 and 2.

Plans with low generic dispensing rates need to ensure that their tiered formularies offer enough incentive for members to choose generics. Small differentials in payment levels are often not enough to influence member purchasing behavior. A differential of $15 or more may be required to have a significant impact on member behavior.

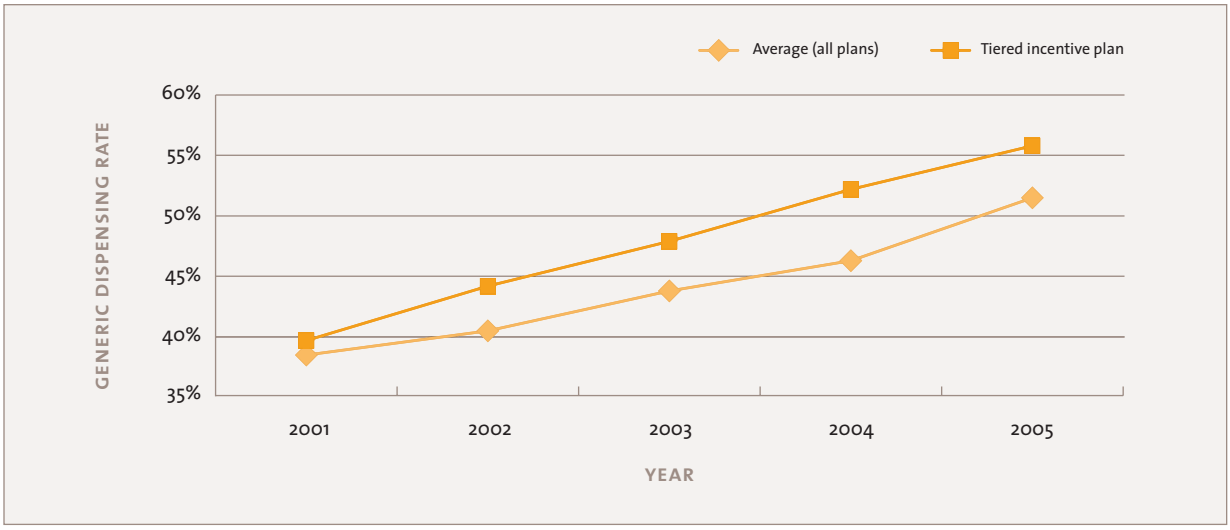
Case study: Tiered incentives for generic drugs

A large employer in the retail industry has maintained an open formulary design that provides strong incentives for generic drug use. The formulary is structured into three tiers—generic drugs, single-source brands, and multisource brands. The plan design includes 25% coinsurance at retail, flat-dollar co-payments at mail, and per-prescription minimums and maximums for retail purchases.

To provide an incentive for generic drug use, this client has maintained strong payment differentials between the first tier (generics) and third tier (multisource brands) in its formulary. For mail-order prescriptions, this has been accomplished by increasing the spread between the fixed-dollar co-payments for these tiers. For retail prescriptions, the plan has increased the spread between the minimum payments and the spread between the maximum payments for these two tiers.

The employer has reviewed and updated these incentives on an annual basis to make sure that they continue to provide a strong inducement to use lower-cost generic drugs. As a result of its efforts, this client has consistently achieved a generic dispensing rate (GDR) that is significantly higher than the average for Medco clients as a whole (Figure 6).

Figure 6. Generic dispensing rate for an open formulary plan with tiered incentives
Source: Medco data



Note: The figure shows the overall generic dispensing rate (GDR) for a large employer that has maintained an open formulary plan with strong tiered incentives for generic drug use. GDRs for this client are compared to the average GDR for all Medco clients for each year.

GENERIC CO-PAYMENT WAIVER

Some plans offer a co-payment waiver as a way of introducing their members to generic drugs. During the initial time period defined by the waiver program, members can get generics for no cost. This is a low-cost way of introducing generics to members who may have been reluctant to switch from a brand-name medication.

Case study: Generic co-payment waiver

A large health plan client wanted to reduce prescription drug costs by encouraging its members to switch from brand-name drugs to generic drugs.

Plan design changes:

- The health plan implemented a co-payment waiver program during the last 3 months of 2004.
- Under the program, plan members had a $0 co-payment for all generic drugs, after meeting any applicable deductibles.

Results:

- The program was successful in encouraging many members to switch to generic drugs. Approximately 22% of members using brand-name medications switched to generic alternatives.
- The plan's GDR increased on a sustained basis. In the quarter immediately preceding the co-payment waiver program, the GDR averaged 47.6%. During the 3-month period of the program, the GDR increased sharply until it peaked in December 2004 at 54.2%. After the program concluded in January 2005, the rate dropped slightly and then settled into a range that was significantly higher than in 2004. During 2005, the plan's GDR averaged over 51%.
- Members saved a total of $17.6 million in out-of-pocket prescription costs during the 3 months the program was in effect. These plan costs were offset by $7.5 million in savings from the increased use of generic drugs during the program, reducing total plan costs for the program to $10.1 million. The temporary bump in plan costs was ultimately mitigated as usage shifted toward lower-cost generic drugs on a long-term basis.

Given the success of the 2004 program, the health plan has decided to implement the co-payment waiver program again in 2006.

MEMBER-PAYS-THE-DIFFERENCE

Member-pays-the-difference is a variation on an incentive formulary that promotes the use of generics. If a member purchases a brand-name drug for which a generic is available, the plan sponsor charges the difference in cost between the brand and the generic—in addition to the co-payment that otherwise applies.

A member-pays-the-difference program effectively limits plan sponsors' financial exposure for multisource brands, while at the same time providing an incentive for members to choose lower-cost generics. Like coinsurance, this program can result in high variability in prescription costs for members.

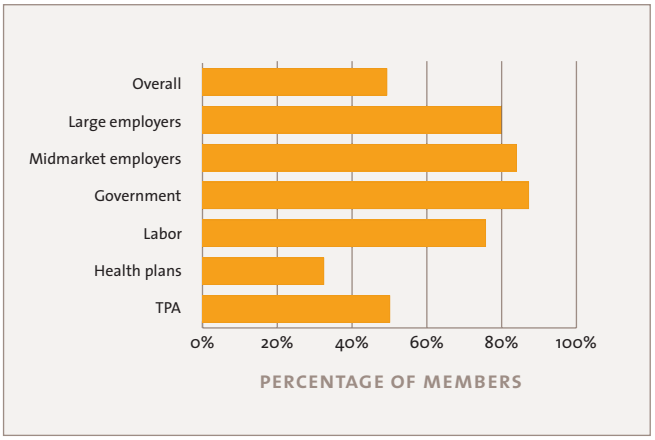
Analysis:

- Employer groups, government plans, and labor plans make the greatest use of member-pays-the-difference programs (Figure 7). About 80% of members in these plans receive this incentive to use generic alternatives.
- Participation in these programs is relatively low in health plans.

Plan considerations:

- Unionized plans are increasingly implementing generic incentive programs as a way to get the most out of their benefit dollar while preserving a quality benefit for their members.
- Some plan sponsors may see member-pays-the-difference as overly punitive for their members. As an alternative, some may wish to consider an incentive formulary with appropriate differences in co-payment levels across tiers.
- The increased availability and use of generics has been a major contributor to declining trend. Emphasis on benefit management options that encourage the use of generics will help to continue this trend. By promoting the use of generics, benefit plans can achieve both immediate and long-term savings.

Figure 7. Plan designs that include a member-pays-the-difference program
Source: Medco data



Note: For each client group, the figure shows the percentage of members who participate in a plan that includes a member-pays-the-difference program. Data shown are for 2005.

MORE WAYS TO CAPTURE GENERICS SAVINGS

Encouraging the use of generic alternatives to brand-name drugs is currently the single most powerful management tool to combat rising prescription drug costs. With $45 billion in brand-name drug patents projected to expire over the next 5 years,[1] plan sponsors need to devise strategies to ensure that they capture as much of these savings as possible.

Beyond the strategies already mentioned—formulary incentives, co-payment waivers, and member-pays-the-difference programs—there are many additional ways to promote the use of generic drugs:

1. Off-patent migration strategies

Plans can develop awareness programs (for physicians) and incentives (for members) that encourage the use of brand-name medications with soon-to-expire patents. For example, plans can move these drugs to a lower tier—in advance of the generic conversion—to help broaden the base of users and increase utilization of the new generics when they become available. Plans may also want to consider contacting high-volume prescribers in advance of the introduction of a major first-time generic.

2. Mail-order incentives

By using a retail-to-mail conversion program or a retail refill allowance, plans can encourage members to fill their maintenance prescriptions through mail order. Prescriptions filled at mail are generally transitioned to new generic products sooner than prescriptions filled at retail.

3. Clinical management programs

Generic drug selection can be encouraged using a step therapy program that requires members to try a clinically appropriate generic drug before providing coverage for a brand-name drug. Targeting specific classes of drugs (such as proton pump inhibitors or cholesterol-lowering agents) can help improve generic dispensing rates and maximize plan and member savings.

4. Brand-to-generic interchange programs

Where clinically appropriate, plans can encourage the use of specific brand-name drugs for which generic alternatives offer a similar treatment response, and they can contact physicians and members regarding the potential savings opportunities. Transitioning members to generics from other brand-name drugs in the same therapeutic class will shift the therapy mix to a lower average unit cost.

5. Dispense-as-written requests

Plans can expedite generic substitution by identifying prescriptions where generic equivalents are available for brand-name drugs, and by contacting physicians and patients to determine whether the substitution would be appropriate. Generic substitution can reduce the out-of-pocket costs for members, while keeping them on essentially the same medication.

6. Education-based communications

Plans can encourage generic drug selection by developing communications for physicians, members, and pharmacists that promote generics as safe and cost-effective alternatives to brand-name drugs. "Report cards" that detail the cost-savings opportunities for members, generic prescription rates for physicians (as compared with their peers), and generic dispensing rates for retail pharmacists (as compared with competing stores) may be effective tools to motivate change.

Mail-order incentives

The cost and quality advantages of mail-order programs are well-known.[2,3] Plans can save up to 10%, on average, through deeper discounts off the wholesale price of drugs. They also benefit from faster and higher generic substitution rates, and they pay fewer dispensing fees (the 90-day supply at mail means fewer refills, on average, than at retail). Automated mail-order pharmacies have also been shown to have an advantage over retail pharmacies in terms of reduced dispensing errors.[3] Plans with heavy mail-order usage typically see improved compliance with formularies and with utilization and safety rules.

Many plan members have an incentive to purchase their prescriptions through mail order, since co-payment/coinsurance levels are often set lower for mail-order prescriptions on a days'-supply basis.

■ RETAIL REFILL ALLOWANCE

Additional incentive programs, such as *retail refill allowance*, promote the use of mail by increasing co-payment costs for maintenance medications purchased at a retail pharmacy after a predetermined number of fills. Until recently, only a few Medco clients used retail refill allowance programs, but the number has grown rapidly over the past few years. In 2005, nearly one-third of clients employed some form of retail refill allowance. Figure 8 shows the percentage of members in each client group that were enrolled in plans with these programs.

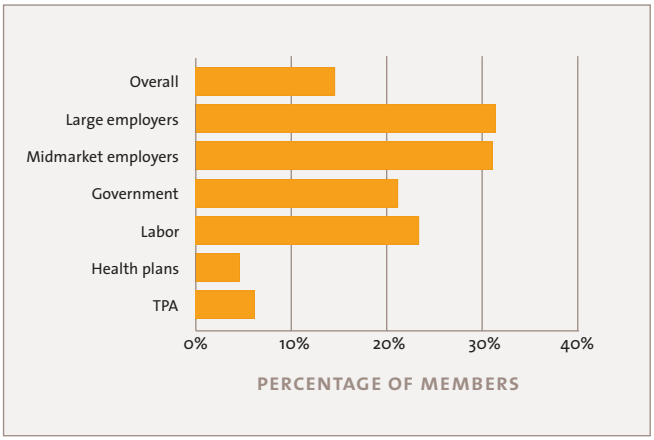
Analysis:

- Employers make the most extensive use of retail refill allowance programs. Over 31% of members in these groups are enrolled in plans that use this mail-order incentive.
- Health plans and TPAs make relatively little use of retail refill allowance programs.

Plan considerations:

- Communications to members are critical to program success. Members need to understand how the allowance plan works and how to get started with mail order.
- Plan sponsors can define the additional member cost share as a fixed-dollar amount or a percentage of total drug cost, up to 100%.
- The health benefit managers of state and local governments must balance the interests of multiple stakeholders, including elected and appointed officials, medical providers, retail pharmacy advocates, unions, employees, and retirees. The retail pharmacy community generally opposes plan design features that favor the use of mail order. However, retail refill allowances can be effective in moving appropriate maintenance prescriptions to the mail-order channel, where plan costs are generally lower, and many government plans have successfully implemented these programs.

Figure 8. Plan designs that include retail refill allowances
Source: Medco data



Note: For each client group, the figure shows the percentage of members who participate in a plan that includes retail refill allowances. Data shown are for 2005.

Case study: Retail refill allowance

For some clients, increasing member cost share and decreasing overall plan costs is not just an option—it is vital to the survival of the business. One employer with a large majority of union employees was faced with this scenario in 2004.

Plan design changes:

- In January 2005, the employer implemented a retail refill allowance to encourage use of the more cost-efficient mail-order channel.
- The retail refill allowance was structured to allow three fills of a maintenance prescription at retail pharmacies. After the third fill at retail, the member has the option of moving the prescription to mail or paying an additional cost share (in this case, 50% of the drug cost) for continued fills at retail.
- The employer also increased the co-payment levels in its plan design. It adjusted the levels of these payments, so that when members shift prescriptions to mail, there are savings for both the member and the plan.

Results:

- Members' use of mail order increased dramatically. Mail-order dispensing increased to 53.9% of the total days' supply dispensed under the plan in 2005—nearly double the 27.7% mail-order utilization in 2004.
- Drug trend decreased significantly, from 20.8% in 2004 to 8.9% in 2005.
- The average discount rate on the plan's drug purchases increased by four percentage points.

MORE WAYS TO PROMOTE MAIL ORDER

As an alternative to retail refill allowances, some plan sponsors may prefer a *retail-to-mail conversion program* that uses outbound mailings and telephone calls to educate members about the benefits of mail. Although this type of program is less effective than retail refill allowances, it can generate conversion rates as high as 6%, yielding up to 3% savings on overall plan costs.

Many clients use *co-payment waivers* to offer an additional incentive for members to convert to mail-order service. Co-payment waivers can be twice as effective as regular mailings in moving members to mail. A waiver of $15 off the regular mail co-payment can generate conversion rates as high as 12%.

Clinical management strategies

Clinical management programs can be used to encourage effective prescribing and dispensing practices. Some of these strategies can lead to savings for plan sponsors, although the opportunities for savings may be less prominent than for cost-sharing strategies, generic incentive programs, and mail-order incentive programs.

PRIOR AUTHORIZATION

When a prescription is filled by the dispensing pharmacist, the claim is reviewed to ensure that it is eligible for coverage under the member's benefit plan. The decision is based on a set of coverage rules that are founded on clinical best practices and that may be tailored to the specific requirements of the plan sponsor. In some cases, the drug may not be covered under the standard rules, or additional information about the member's diagnosis or treatment may be required before the coverage decision can be made. In these cases, *prior authorization rules* define the conditions under which the plan sponsor will authorize the medication to be covered under the plan.

Prior authorization rules are typically specified on a drug-by-drug or a class-by-class basis. Some specific high-cost medications and nonformulary medications require prior authorization whenever dispensed. An automated form of prior authorization uses logic-based intelligence to determine immediately whether a member qualifies for coverage. In other cases, contact with the prescribing physician may be required to obtain the necessary information about the role of the medication in the member's treatment plan.

Prior authorization can be used to override standard coverage rules—such as quantity or dosage limits. For example, the coverage rules for *Xifaxan*® include quantity limits that support a standard course of treatment for travelers' diarrhea (200 mg three times daily for 3 days). Prior authorization can be used to override this limitation for a member who is prescribed *Xifaxan* for the treatment of hepatic encephalopathy. For this indication, the prior authorization rule would support coverage for long-term use of the medication at a higher quantity (up to 1200 mg) per day.

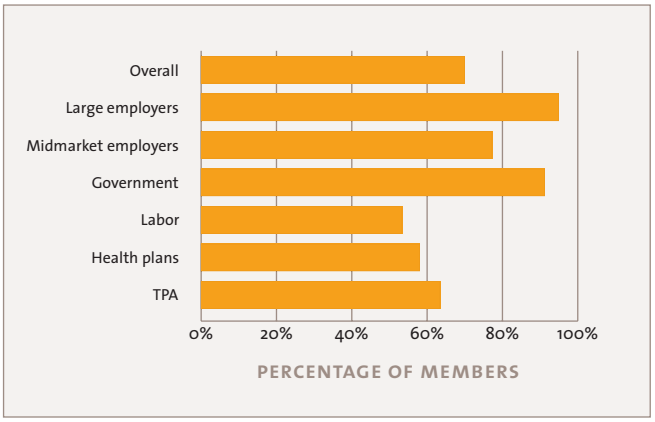
Prior authorization rules can also be designed to provide utilization management for medications that may be overused, that are indicated for use only under very specific conditions, or that may be used for conditions that a plan would not normally cover (such as the use of *Retin-A*® for cosmetic purposes).

Step therapy is an approach to prior authorization in which members are required to try certain lower-cost drug options prior to receiving coverage for more expensive drugs in the treatment category. For example, coverage of angiotensin II receptor blockers (ARBs) for the treatment of hypertension could be limited to specific types of patients who do not respond successfully to angiotensin-converting enzyme (ACE) inhibitors. ARBs tend to be more expensive than ACE inhibitors, many of which are available in generic form.

Analysis:

- About 70% of members participate in plans that incorporate one or more prior authorization rules (Figure 9).
- Employers and government plans show the highest use of prior authorization rules. Use of these rules is lowest in labor and health plans.

Figure 9. Plans that include prior authorization rules
Source: Medco data



Note: For each client group, the figure shows the percentage of members who participate in a plan that includes one or more prior authorization rules. Data shown are for 2005.

Plan considerations:

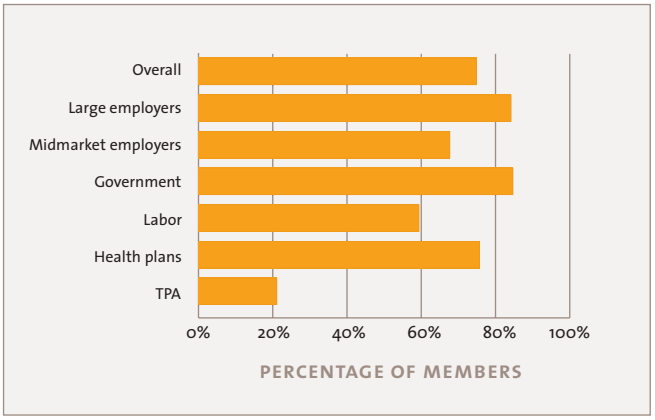
- Step therapy programs may be combined with other plan design features, such as tiered formularies, so that clinical rules and financial incentives are appropriately aligned.
- When a prescription drug becomes available over the counter, plan sponsors may limit coverage for similar drugs in the same class, using prior authorization to administer the coverage rules. For example, when *Prilosec*® became available over the counter, some plans applied prior authorization rules to specific drugs in the same therapeutic class (such as *Nexium*®), while others implemented rules for all drugs in the class.
- Some members may view prior authorization as intrusive or inconvenient, because it involves an additional administrative step before a prescription can be filled. However, it can also be seen as enabling coverage rather than limiting it. Without the coverage precision afforded by prior authorization, plan sponsors could decide to not cover certain drugs at all.

DISPENSING QUANTITY LIMITS

Dispensing quantity limits specify the amount of medication that may be dispensed under a single co-payment. These limits can be used to reduce the likelihood of overutilization or stockpiling.

For example, limits can be used to manage the dispensing of estrogen patches, which are generally applied only once or twice a week. Without any quantity limits, a member could potentially obtain more than four or eight patches as part of a 30-day prescription at retail. Under a dispensing quantity rule, coverage would be provided for only four or eight patches—an amount more consistent with product guidelines and clinical best practices.

Figure 10. Plans that include dispensing quantity limits
Source: Medco data



Note: For each client group, the figure shows the percentage of members who participate in a plan that includes one or more dispensing quantity limits. Data shown are for 2005.

Analysis:

- Use of dispensing quantity limits is relatively high for all client groups except TPAs (Figure 10).
- Dispensing quantity limits are commonly used in government plans, including state-run Medicaid plans.

Plan considerations:

- Dispensing quantity limits are often combined with prior authorization rules. Members who request coverage for additional quantities per co-payment would need to obtain prior authorization. Alternatively, they could pay another co-payment to obtain an additional quantity (within the specified limits and subject to drug utilization review guidelines).
- Dispensing quantity limits are useful for drugs that are used on an as-needed basis, such as those used to treat migraine headaches. The majority of people with migraine headaches experience four or fewer episodes per month,[4] so costs can be reduced by limiting the quantity of dispensed drugs to the amount that is most commonly needed.
- Quantity limits may also be useful for drugs that are typically used for a short, well-defined course of therapy, such as antibiotics.

DOSE OPTIMIZATION

Dose optimization programs are designed to lower the cost of care by reducing the number of tablets or capsules that are dispensed, while maintaining the same total daily dose for the patient. These programs reduce cost by shifting utilization from lower-strength formulations to higher-strength formulations that can be taken less frequently.

For example, taking a 100-mg tablet once per day may provide essentially the same therapeutic benefit as taking a 50-mg tablet twice per day. If the higher-strength and lower-strength tablets are priced similarly, dose optimization can help reduce plan costs by encouraging use of the higher-strength alternative. Common categories of drugs for which dose optimization is an option include drugs to treat high blood pressure and high cholesterol.

Analysis:

- Many plans do not yet take advantage of dose optimization programs. Less than 5% of members are in plans that incorporate this cost-saving strategy.
- Large employers have the highest level of participation in dose optimization programs.

Plan considerations:

- As part of an overall clinical management plan, dose optimization rules can deliver savings with minimal member disruption. Many members may prefer the convenience of taking only one pill a day instead of two.
- Dose optimization is therapeutically appropriate and financially beneficial for only a small number of drugs, so the opportunities for savings are limited. However, these savings apply to some widely used classes of maintenance drugs, including antihypertensives and lipid-lowering drugs.
- In a *tablet-splitting program*, costs are reduced by dispensing half the quantity of a higher-strength tablet in place of the lower-strength tablets that were prescribed. Members are encouraged to split the tablets to achieve the prescribed daily dose. Tablet-splitting programs can be beneficial when tablets are well-scored and pricing is relatively similar across different strengths of the same drug. These programs provide members with the option of requesting approval for lower-strength tablets if they are unwilling or unable to break their tablets.

Trend to watch: Medicare prescription drug benefit

The introduction of the Medicare Part D prescription drug benefit in January 2006 has had a profound impact on pharmacy benefits for retirees and the plan sponsors who provide coverage for them. The basic Part D drug benefit includes many of the cost management tools described earlier in this section, including coinsurance, deductibles, and defined coverage exclusions. Plans under this benefit include formularies that provide access to a wide range of medications, while incorporating incentives to manage costs. Plan designs are reviewed and approved by the Centers for Medicare and Medicaid Services (CMS).

Employers, government plans, and labor groups were faced with five main options:

- Accept a federal retiree subsidy to remain the primary payor.
- Become a prescription drug plan (PDP) sponsor for their own Medicare-eligible retiree populations.
- Provide "enhanced" coverage through an outside PDP.
- Offer secondary coverage that supplements Part D coverage.
- Drop prescription drug coverage for retirees.

Health plans have had to create their own stand-alone PDPs or offer benefits through Medicare Advantage prescription drug (MA-PD) plans under Medicare Part C.

For the first year (2006), Medco clients decided to offer the following types of prescription benefit coverage:

- Most employers, government plans, and labor plans elected to retain coverage. In these client groups combined, over 95% of Medicare-eligible members enrolled in primary plans or group-enrolled plans (enhanced or stand-alone PDPs).
- Several government and labor plans chose to cover retirees through group-enrolled plans. In these client groups combined, approximately 13% of members participate in group-enrolled PDPs.
- No government or labor plans dropped prescription drug coverage. Several plans offer members some form of secondary coverage to supplement Part D benefits.
- All health plan clients implemented stand-alone PDPs or MA-PD plans.

Managing specialty drugs: Case studies in personalizing healthcare

With more than 350 new biotechnology medications in late-stage clinical development,[5] effective management of specialty drugs is more important now than ever. The development of new specialty medications offers hope for members who may previously have had few pharmaceutical options, but it also raises significant challenges for plan sponsors to provide access to these medications without overburdening the benefit.

Traditional strategies for cost management and therapy management can all be applied to the management of specialty drugs. However, given the specialized needs of many patients using these medications, effective cost management will require more intensive oversight and more personalized delivery of healthcare.

COST MANAGEMENT STRATEGIES

Historically, managing specialty pharmacy expenses was focused on controlling the unit costs of the few available products. In most therapeutic categories, competing products (whether brand or generic) were generally unavailable. Today, however, there are more competing brand-name products in many therapeutic categories, which provides an opportunity to use formulary management techniques to influence product selection and lower plan costs.

Specialized strategies for cost management include:

- **Preferred brand-name products.** In incentive formularies, plans may assign selected specialty products to a lower tier than nonpreferred specialty products. The lower co-payment or coinsurance levels will give members an incentive to use options that are more cost-effective for the plan, while reducing members' out-of-pocket expenses.
- **Fourth formulary tier.** For high-cost specialty medications, a traditional flat-dollar co-payment is likely to represent only a small fraction of the medication's cost. Plans can use a fourth tier to establish separate co-payment or coinsurance levels for selected specialty products. This provides an opportunity to differentiate the co-payment or coinsurance levels that apply to specialty drugs from those that apply to traditional medications. However, there is a risk with this strategy, since a higher cost-share for these drugs may make them unaffordable for some members. If members stop taking their medication, healthcare expenses under the medical plan could increase.
- **Distribution channel management.** For specialty drugs, the opportunities for cost management go well beyond the ingredient costs of the drugs themselves. It is also important to manage the costs of the distribution channel, including the costs associated with storage and delivery, the costs of related supplies (such as syringes and infusion devices), and the costs of patient care services. An effective specialty distribution channel will provide a competitive unit price for the drug, as well as a set of therapy management services that deliver the best total cost.

With few exceptions (such as leuprolide and ribavirin), specialty medications are not available in generic form. As a result, the opportunities for cost management through increased generic use are very limited for specialty products.

CLINICAL MANAGEMENT STRATEGIES

As the options for specialty drug therapy expand, traditional strategies for utilization management (such as step therapy) can be applied more broadly to manage the costs of specialty drugs. Intensive therapy management services are also essential to cost-effective care for patients using specialty medications.

Specialized clinical management strategies include:

- **Prior authorization programs.** These programs can help ensure appropriate dosing in the administration of specialty drugs, thereby reducing opportunities for overuse and waste.
- **Step therapy.** As part of a prior authorization program, plans can take a step therapy approach with specialty medications when clinically appropriate. For example, plans could limit the use of *Xolair*® to patients whose allergic asthma has not been successfully controlled by prior treatment with inhaled corticosteroids alone.
- **Patient care services.** For specialty drugs, patient care services are essential to managing treatment cost-effectively. These services may include patient education, assistance with drug administration, guidance on medication compliance, and help with side-effects management.
- **Integrated health and safety monitoring programs.** These programs take an integrated look at a patient's pharmaceutical care, medical care, and laboratory results to ensure that the patient's treatment is consistent with clinical best practices. The programs are designed to identify patterns of care that may pose unnecessary risks to members, address any gaps in current care, and reduce the plan sponsor's exposure to unnecessary healthcare costs.

Therapy management programs are designed to manage the total cost of pharmaceutical care. As a result, when comparing the cost of different therapies, it is important to include all associated administration fees, including infusion charges, supply costs, and laboratory expenses—in addition to the cost of the medications themselves.

CASE STUDIES: A CLOSER LOOK AT COORDINATING SPECIALTY CARE

One of the challenges with high-cost biologics is to ensure that members receive the full clinical benefit of their medications, while maintaining affordability to the plan. For specialty drugs, this may require investing in therapy management services that are tailored to the needs of the individual patient. Personalized healthcare services can be a cost-effective way to reduce overutilization, waste, and the overall costs of care.

Case 1: Reducing waste through personalized dosage management

Appropriate Factor VIII dosing for hemophilia patients depends on the individual product prescribed, the location and severity of the bleeding episode, and the body weight of the patient.[6] Factor concentrates are not provided in consistent dosages, but in varying assay ranges, so products need to be selected carefully. Reconstituted factor must be infused within 3 hours, so full vials—rather than a portion of a vial—need to be administered to reduce the likelihood of waste.

In order to fill prescriptions in the most cost-effective manner, it is necessary to maintain a robust inventory of different factor concentrates so that the vial sizes most closely matching the desired dosage can be used to fill the prescription. Although administering a higher dose than necessary will not harm the patient, overutilization of factor concentrates can increase annual treatment costs by 12% to 25%.[6]

A specialty pharmacy that can provide good factor assay matching can save plan sponsors a significant amount of money. The following are the results of a quarterly report for a large health plan client of Accredo Health:

Dose to assay report
Reporting period: April 1, 2005, to June 30, 2005

Total prescriptions	208
Total patients	89
Total prescribed units	4,677,844
Total dispensed units	4,700,260
Variance in units	0.48%
Total cost (including the 0.48% variance)	$4,700,260.00
Projected cost for 10% variance	$5,145,628.40
Projected savings	**$445,368.40**

As noted in this client's report, close management of factor assays achieved near-zero variance (less than 0.5%) from the required units, resulting in an estimated savings of almost $2 million on an annualized basis. The savings calculation makes the conservative assumption that treatment costs would be 10% higher without proper factor assay matching.

Case 2: Reducing costs through personalized patient services

A 79-year old woman with pulmonary hypertension was prescribed an infused prostacyclin. The infusion process is complex; two pumps must be available at all times, since the drug's half-life is 2 to 7 minutes, and any interruption of the infusion may lead to life-threatening rebound pulmonary hypertension. Also, the medication must be kept cold during the continuous 24-hour infusion, and the central line must be closely monitored and cared for. Due to the complicated nature of the infusion, a caregiver is often educated along with the patient to provide support and assistance.

Finding a caregiver for this patient proved difficult. Her children lived out-of-state, none of her neighbors or friends were available or able to help, and three nursing agencies declined to provide the service. The assisted living facility where the patient resided agreed to help, but planned to charge the patient $200 per day for nursing care, plus any additional costs. The patient elected not to use this service.

To ensure that the medication was administered properly and assist the patient in becoming independent, a nurse from Accredo Health drove 5 hours each day to visit the patient and provide the necessary training and support. During these visits, she also trained the fire department and paramedics on what complications to expect and how to help the patient if the infusion process was interrupted. After 14 days of training, the patient was able to administer the medication independently, and she remained self-reliant for 3 years with the support of regularly scheduled calls from her Accredo nurse and pharmacists.

The initial investment of the nurse's time may seem excessive, but it was actually a cost-effective solution to the problem. Pulmonary hypertension requires lifelong therapy, so it was especially important to help establish the appropriate dosage and administration process at an early stage. The intensive monitoring and training reduced the likelihood of wastage of this expensive therapy, which costs about $194 per day (at wholesale prices) for the average patient. It also reduced the likelihood of serious side effects that could require expensive medical care. These savings can more than make up for the expense of the ongoing specialized care.

■ PERSONALIZING CARE

Providing a valuable specialty pharmacy service for plan sponsors and patients goes beyond providing needles, sterile dressings, gloves, and tape. A specialty pharmacy provides value by coordinating care across all services, to meet the individual needs of the patient. While the next wave of personalized medicines is still years away, specialty pharmacy is already personalizing healthcare.

Measuring your *PBM DNA*™

A number of interrelated factors influence the coverage decisions plans make. These range from member demographics to the ethical responsibility to balance member care with the plan's finite financial resources. Does the plan focus primarily on treating serious illnesses, or does it also cover drugs that enhance health, function, and appearance? Is the plan willing to pay for nontraditional or even experimental interventions in certain circumstances, or does it only cover time-tested treatments supported by evidence-based medicine?

These decisions are influenced by the specific circumstances of each plan. Such circumstances may include whether the plan sponsor faces political or contractual constraints in designing its benefit, whether it is concerned with providing a generous benefit to attract new employees, or whether it is simply trying to keep a relatively stable workforce healthy and productive. These types of coverage determinations help determine a plan sponsor's overall benefit philosophy.

DIGGING DEEPER INTO BENEFIT PHILOSOPHY

Seeing what other plan sponsors are offering is informative, but it may not help an individual plan determine what benefit management approaches are best matched to its personal philosophy. Benchmarking against other plan designs in the industry may miss some of the sociological and ethical concerns that influence a plan's benefit decisions. These factors help explain why there is significant variation in the plan designs offered within each of the client groups characterized in the previous sections of this report.

Some plan sponsors are willing to employ as many pharmacy benefit management (PBM) tools as possible in an effort to keep costs down. Others are willing to absorb cost increases rather than impose more restrictions or a greater financial burden on their members. An employer with a largely unionized workforce may not be as willing or as able to make changes as a similar employer with a nonunion workforce. Because these kinds of differences go beyond what a simple analysis of peer comparisons can tell us, it is helpful to consider how plan sponsors differ at an individual level. This can be done by looking at their **PBM DNA**—the characteristics that define how and why they make their benefit management choices, as well as the nature of the choices themselves.

We have identified a number of key factors that help determine a plan's underlying genome. Using these to identify your **PBM DNA** may help you:

- Measure your benefit offerings against those of like-minded plan sponsors to evaluate potential opportunities.
- Better select the plan design that is right for you and your members from among the many options available.
- Evaluate how changes in benefit strategy might improve your plan.

KEY FACTORS THAT DETERMINE BENEFIT PHILOSOPHY

In the biological sciences, DNA base pairs are the sequences that help define the structure and function of an organism. (See the section on "Personalizing medicines," beginning on page 60.) Similarly, the following components of **PBM DNA** define the structure and function of a plan's benefit:

- **Ability to make plan changes.** To what degree are you able to change your benefit structure? Are there bylaws, regulations, contractual obligations, or other factors that restrict the types of changes you can make? Plans offered by self-insured employers are often less restricted than plans that require contract approval by union membership, benefit boards, or regulatory bodies.

- **Approach to cost containment.** The primary approach to cost containment often has the most impact on how a plan sponsor will structure a prescription drug benefit. Does your plan favor controlling costs through incentives such as the use of coinsurance, tiered co-payments, deductibles, or consumer-driven options? Or do you primarily rely on managing coverage through measures such as prior authorization, dispensing quantity limits, and dose optimization?

- **Receptiveness to new benefit management tools.** Is your plan an early adopter, willing to implement plan design strategies that are more innovative? Or do you typically take a "wait-and-see" approach, relying on established plan management strategies? Plans that are willing to try new programs before results are available are more innovative in style. Other plans may wait a year or more before signing on for new benefit strategies—perhaps because they only consider plan changes annually, or because significant changes have to be negotiated as part of a contract, or because they prefer to see proven results before signing on to a new program.

- **Primary audience.** Do you prefer strategies that involve contacting physicians whenever possible, or strategies that involve member communication? Many employers, collectively bargained plans, and state and local government plans do not like to manage benefits by directly involving the members. Health plans and other organizations may err on the side of impacting members, preferring benefit management approaches that have a less direct effect on physicians.

These four elements of **PBM DNA** can be summarized as follows:

Elements that define the genotype	DNA base pair	
Ability to make changes	Nonrestricted	Restricted
Approach to cost containment	Cost	Utilization
Receptiveness to new tools	Innovative	Established
Primary audience	Members	Doctors

APPLYING YOUR *PBM DNA*

After determining their individual genome using the criteria identified above, plan sponsors can compare their benefits to plans that are based on a similar philosophy. By comparing programs and plan performance, a plan sponsor may decide to implement programs that are consistent with its benefit philosophy and have helped others be successful.

A plan sponsor may have multiple genomes depending on the diversity of its membership. For example, a plan sponsor may support both union and nonunion workforces, or it may support multiple organizations with different benefit philosophies. Also, unlike the DNA base pairs that form the human genome, some of the fundamental components of **PBM DNA** may change over time. In general, a plan's approach to cost containment and its receptiveness to new strategies may be more amenable to change. A plan's primary audience and its ability to make changes may be ingrained in its business model, so these factors may be less likely to change.

We can now apply these concepts to a hypothetical plan sponsor. Consider, for example, a nonunion employer with the following **PBM DNA**:

Elements that define the genotype	DNA base pair	
Ability to make changes	**N**onrestricted	Restricted
Approach to cost containment	**C**ost	Utilization
Receptiveness to new tools	Innovative	**E**stablished
Primary audience	**M**embers	Doctors

Plan sponsors with this genome—**NCEM**—might have benefit designs with the following features:

- Incentive formulary
- Tiered co-payments or coinsurance
- Retail refill allowances for members taking long-term medications
- Prior authorization for several classes of medications

The employer in our example could review the benefit designs of plans with the same **NCEM** genome. The employer may find that it does not currently offer a program that is commonly offered by plans with the same genome, and it may therefore be missing an opportunity to better manage its benefit.

The table below summarizes an opportunity analysis for three hypothetical clients. It includes the feature set that is best aligned with each genome (the benefit design "according to DNA") and the client's current ("actual") benefit design. The employer in our example (Client A) may be missing an opportunity to implement an incentive formulary design. The two clients with different genomes (Clients B and C) may also be missing opportunities to improve the performance of their plans.

Client	PBM DNA	Benefit design	Retail refill allowance	Member-pays-the-difference	Prior authorization	Incentive formulary design
Client A	NCEM	According to genome	X	X	X	X
		Actual	✓	✓	✓	Missed opportunity
Client B	RUEM	According to genome	O	O	X	X
		Actual	Potential opportunity	Potential opportunity	Missed opportunity	✓
Client C	RCIM	According to genome	X	X	X	X
		Actual	Missed opportunity	✓	✓	✓

X – Plans with the indicated genome typically have this feature. For clients with the same genome who do not currently have this feature, it represents a **missed opportunity** that may provide value to the plan.

O – Plans with the indicated genome do not typically have this feature. For clients with the same genome who do not currently have this feature, it represents a **potential opportunity** that may add value to the plan.

✓ – The client's plan includes this feature.

These clients could use data analysis and modeling tools to evaluate the potential cost impact and member disruption associated with implementing the programs that they do not currently offer. Their account team could provide information about how they might implement these programs, what difficulties they might encounter, and how these issues are typically resolved. This background and analysis would give the client a more complete understanding of what it would take to add the program—and perhaps help them avoid some of the same pitfalls that other plan sponsors have experienced.

Case study: Modeling a plan change

Imagine that Client A is a large employer with 130,000 members and $75 million in annual drug spending. The benefit plan currently uses a two-tier open formulary design with co-payments of $10 (generic) and $20 (brand) at retail and $20/$40 at mail.

An analysis of other clients with the same NCEM genome showed that many of them offer an incentive formulary with three or more tiers. By switching to an incentive formulary design, Client A could strengthen the incentives for its members to choose generic drugs and preferred brands, especially for mail-order prescriptions.

Using a modeling analysis for Client A, we can estimate the impact of switching from a two-tier open formulary to a three-tier incentive formulary. For example, imagine that the client switched to a standard incentive formulary design with co-payments of $10 (generic), $20 (preferred brand), and $30 (nonpreferred brand) at retail, and $24/$50/$90 at mail. The modeling analysis shows that Client A could save money by making this change. The projected savings with the new plan design would be about $2.6 million per year, or 3.5% of total plan cost.

The estimated savings could be even higher if a significant number of members shift their usage toward preferred drugs in response to the new incentives. Following a change from a two-tier to a three-tier formulary, many members are likely to shift from nonpreferred drugs (tier 3) to preferred drugs (tiers 1 and 2), and they are unlikely to stop taking their medications altogether.[7] In contrast, more dramatic changes in plan design can sometimes lead a significant number of members to discontinue their therapy.[7]

Choosing which programs to implement is not an exact science. While the **PBM DNA** model hopefully adds some precision to these kinds of decisions, it does not provide the same predictive value that human DNA can. Its primary value is in identifying opportunities for management strategies that a plan may not otherwise have tried. If plans with the same benefit philosophy have tried and succeeded with a program, it may be possible for another plan to find a way to adopt the same program.

Science has begun personalizing healthcare to meet the individual patient's needs. Similarly, plans will need to become more individualized in how they address opportunities for improvement in benefit design. A plan's **PBM DNA** is at the core of how it determines what choices it will make.

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