A National Perspective
The Number One Priority Hasn’t Changed.

In a recent survey of employee benefit specialists, controlling the rising cost of health benefits ranked #1 in priorities for 2004—a position it has held for the last five years. Employers (and the national economy) have been hit by six years of accelerating growth in overall healthcare spending. Numbers for healthcare spending in 2003 are expected to show a marked reduction in rate of growth, a welcome change attributed in large part to slowdowns in spending growth for hospital care and prescription drugs. The single-digit pharmacy benefit trend in the Caremark Inc. Book of Business was among the lowest reported in the nation (see Figure 1). By comparison, the Centers for Medicare and Medicaid Services estimated 2003 national growth in drug spending at 13.4%.

In contrast to benefit managers, employees ranked managing healthcare costs #5. Not surprisingly, in 2004, many employers hope to bring those priorities into greater alignment—promoting increased consumerism ranked second among their benefit priorities.

Focus on the Consumer
It’s clear that the shift to the consumer that began in earnest in 2003 will gain momentum in 2004 as employers struggle to find ways to continue to offer health benefits. Consumers are paying a larger share, and they are increasingly exposed to actual costs, particularly for prescription drugs. In 2003, many American businesses increased premiums, and nearly 80% of workers faced a deductible for healthcare expenses. In the Caremark Book of Business, more than 90% of participants were in a 2- or 3-tier co-pay plan, compared to 86% of all U.S. workers. CONTINUED PAGE 3.
Trend management for our clients is our primary goal at Caremark. For 2003, clients responded to our recommendations for aggressive management measures, and they—and we—ended the year with one of the lowest trend numbers in the industry.

Our single-digit trend in 2003 reflects a number of factors.

- Most importantly, growth in utilization, at 1.6%, was minimal compared to the 2002 number, 5.3%.
- The introduction and utilization of generics and OTC versions of brand blockbusters helped to slow trend.
- Price increases, the dominant driver in 2002, reverted to more normal levels, although they are still higher than inflation in the U.S.
- Anticipated blockbuster drug introductions didn’t meet expectations, reducing the impact of new brand drugs.
- Biotech trend continued to grow; management measures helped to hold spend in this category for Caremark clients.
- Plan sponsors made significant changes in plan design, increasing the use of both mail service and generics, successfully driving behavior shifts in their overall participant populations.

At 9.3%, pharmacy benefit trend in the Caremark Book of Business for 2003 is among the lowest reported in the industry.

Figure 1

9.3% Trend

3.5% Price

4.2% Product

1.6% Utilization

Inflation
- Price Increases
- Delivery Systems
- New Generics

New Drugs
- Brand
- Biotechs

Drug Mix
- Generics
- Brands
- Biotechs

Participants
- Prescribers
- Plan Sponsors
- Politics
A National Perspective

CONTINUED FROM PAGE 1

While the goals of increasing employee cost share and consciousness have been widely embraced, full-fledged consumer-directed health (CDH) plans have met slower acceptance. CDH plans combining a high deductible with an employee-controlled spending account have not yet been proven to be an effective long-term cost-control strategy. While employers are more willing than ever to consider plan alternatives to cope with cost increases, many are taking a wait-and-see approach to CDH plans.

Reaching the Consumer

As consumers assume more costs, they have become the focus of decision support efforts. Employers, health plans and pharmacy benefit managers are providing more cost and health information, while pharmaceutical firms have increased their direct-to-consumer (DTC) efforts to help their products achieve blockbuster status. In 2003, even the FDA went straight to the consumer with ads supporting the use of generics.

Are their efforts having an effect? According to one study, every dollar spent on DTC pharmaceutical advertising in 2000 yielded more than $4 in additional sales for prescription brand name drugs that year.7 And there are signs that consumers are starting to look for less expensive drug choices. 2003 saw considerable growth in the utilization of generics. After the introduction of Claritin® OTC, sales for the prescription allergy category dropped, presumably due, at least in part, to migration from the prescription product to the OTC versions. Consumers are also taking matters into their own hands—regardless of safety concerns. It’s estimated that the sales of re-imported drugs from Canada doubled in 2003 to $1.1 billion.8

As your pharmacy benefit manager, Caremark is committed to helping you understand and manage your drug trend. Healthcare is a dynamic environment. All of us—plan sponsors, providers, insurers, and benefit managers—will face new challenges and consider new strategies in the months ahead. In the following pages we share insights gained from an analysis of trend drivers in the Caremark Book of Business in 2003, and we look ahead to 2004 and beyond to help you plan to meet the challenges, evaluate the strategies, and achieve your goals.

Trend—the annual increase in the cost of providing prescription benefits to plan participants—is calculated as gross cost per employee per month in the Caremark Book of Business. Gross cost represents total prescription cost—participant and payer portions. Trend has three major drivers:

The price of drugs—the increase in the cost for brand and generic drugs.

The products used—the mix of brands, generics, biotechs, and new introductions.

Levels of utilization—the volume of prescriptions used, a measure of how often and how many participants use prescription medicines. Utilization is calculated as days supply per eligible cardholder per year.

Book of Business—In general, “Book of Business” represents the Caremark client base for the specified time period.
CONTINUED FROM PAGE 2

Every year has its own trend story. 2003 was marked by unexpected results in research, some surprisingly swift moves by the FDA, continuing biotech breakthroughs, and lackluster debuts of would-be brand blockbusters. Successful management through partnership with Caremark helped our Book of Business reduce the impact of these industry events and achieve the first single-digit trend in four years. In the pages that follow, we will examine the effect of each of the major drivers of trend in 2003.

**Breakdown of Trend Drivers 2000-2003**

*Figure 2*
In 2003, a variety of forces worked together to produce the first single-digit trend in four years.
Utilization, the Impact Opportunity

As a driver of trend, utilization presents a greater impact opportunity to the plan sponsor than either price or product. A number of variables affect utilization—participants, prescribers, plan sponsors, and politics. In 2003, several forces converged, resulting in a favorable rate of utilization growth compared to recent years. Importantly, plan sponsors were significantly more active in 2003 than in 2002, making more aggressive changes in plan design and employing a variety of strategies to increase participant cost share and awareness.

Politics
High prices for prescription drugs have been a hot topic of conversation in Washington. The FDA announced a number of tactics to help lower prices, including expediting approval of generics and approving the over-the-counter (OTC) sale of selected prescription brand drugs, starting with blockbusters Claritin® , a non-sedating antihistamine (NSA), and Prilosec™, a proton pump inhibitor (PPI) indicated for ulcers and gastroesophageal reflux.

Claritin® OTC became available in all prescription strengths in late 2002. OTC versions of the generic loratadine followed soon after. By Q4 2003, more than 50% of previous Claritin® users in the Caremark Book of Business had moved out of the prescription allergy market (see figure 3). Although some Claritin® users shifted to other prescription allergy products, migration within the category to alternative prescription products was smaller than expected, resulting in a 17% negative cost trend for the LNSA (low/non-sedating antihistamine) class in the Caremark Book of Business.

Not every brand-to-OTC introduction will offer the same savings to plans. The introduction of Prilosec™ OTC, with a limited indication and restricted to short-term therapy, resulted in moderate shifts in the prescription category (see page 18 for more information on Prilosec™).

Figure 3
More than half of Claritin® users left the prescription allergy market after the introduction of Claritin® OTC in late 2002.
Prescribers
Medical research often serves to affect utilization. In recent months, for example, one study linked depression with heart disease and another suggested that people with diabetes could benefit from regularly taking statins—in both cases potentially increasing the market for drugs in top-selling categories. In 2003, however, the results from research on hormone replacement therapy (HRT) substantially reduced utilization.

Hormone replacement therapy prescriptions drop. HRT has long been considered to provide some protection against cardiovascular disease for postmenopausal women. In the last few years, however, results from the Women’s Health Initiative (WHI) and the Heart and Estrogen/Progestin Replacement Follow-up Study (HERS II) showed that HRT actually increases the risk of certain types of cancer and cardiovascular disease. Since the results were released, prescriptions for HRT have dropped by more than 30%—helping to reduce utilization trend in 2003. Increases in the utilization of other osteoporosis drugs somewhat offset the reduction in HRT.

Advertising and education efforts reach physicians. Most pharmaceutical advertising targets physicians, but direct-to-consumer (DTC) advertising has steadily claimed a larger share of the pharmaceutical marketing budget since the 1990s. DTC advertising generally aims to encourage consumers to bring questions about specific products or health problems to their physician, and research indicates that it has been extremely effective. In a recent study, 85% of consumers said they had seen or heard an ad for a prescription medicine; 30% said they had talked to a doctor about an advertised drug; and 44% of those who had discussed a medication with their physician received a prescription for it—meaning that 13% of all Americans have discussed an advertised drug with a physician and received a prescription for the drug.9

Increasingly, pharmacy benefit managers (PBMs) and plan sponsors are also trying to reach the physician through the participant. For example, educational resources, such as the Caremark Count on Generics™ program, provide participants with information on drug costs and the value of generics and encourage them to ask their doctor to prescribe formulary or generic medicines. While it will be more difficult to track the effects of these programs on consumer behavior, plans and PBMs have additional ways to effect participant behavior change.

Plan Sponsor and Participant
Effecting participant behavior change was a major concern among plan sponsors in 2003. Plan sponsors made more plan design changes, transferred a higher percentage of costs to participants, and provided education on lower-cost prescription alternatives in order to encourage cost-conscious prescription decisions.
Participants pay a larger share. In the Caremark Book of Business, the participant cost share increased from 20.2% in 2002 to 21.6% in 2003. Average co-pay increased by 12%. More than a quarter of Caremark participants had co-insurance in 2003; the number jumped from 21% in 2002 to 26%. The percentage of Caremark participants with a deductible increased to 13% in 2002, and continues to grow (see figure 4). Increasing participant cost share was one reason that net trend in 2003 at 7.7% was lower than gross trend, 9.3% (see figure 5).

**Figure 4**
With plan design changes, participant cost share increased from 20% to 22% in the Caremark Book of Business in 2003.
Figure 5
Net trend incorporates participant out-of-pocket cost. The 7.7% net trend in 2003 reflected greater participant responsibility for cost share and illustrates that cost share is in line with rising costs.

Figure 6
This graph plots percentages of clients who made changes against their trend results. On average, clients who implemented plan design changes achieved trend 4% lower than those who did not.
Make sure utilization reduction is appropriate. As mentioned earlier, increasing participant cost share was a dominant strategy for plan sponsors across the U.S. in 2003. And trend numbers and polls indicate that the strategy was successful both in reducing benefit cost to plan sponsors and in encouraging participants to ask for and choose less expensive alternatives among their prescription choices. Unfortunately, polls also indicate that some consumers responded to increased prescription costs by reducing dosages or foregoing refills of prescribed medication, particularly for preventive medicines such as antihypertensives and cholesterol-lowering drugs. Lower-income consumers with multiple health problems are at particular risk.

Non-compliance with prescribed therapies can increase the risk of higher medical costs over the long term. In the short term, non-compliance can contribute to increased absenteeism and lowered productivity. As plan sponsors increase participant cost share, it’s important to target discretionary spending, identify high-risk participants, and support compliance by providing information on choosing the most cost-effective prescription alternatives.

Programs support cost-effective and appropriate drug choices. Caremark clinical pharmacy and health management programs serve to educate participants on the importance of compliance. The vast majority of plan sponsors in the Caremark Book of Business have CustomCare programs, which review prescriptions and identify opportunities to suggest alternative therapies to prescribing physicians. To encourage utilization of cost-effective generics or preferred brand medicines, more than half of Caremark participants have plans with a DAW (dispense as written) penalty in place, which requires that participants pay a penalty for choosing a brand-name drug when a generic is available. The percentage of participants in plans with therapy protocols more than tripled in 2003. Therapy protocols target excessive and unnecessary drug utilization and serve to counteract demand resulting from direct-to-consumer advertising.
As we have seen, a number of factors helped lower utilization in 2003. As a plan sponsor, you know that you can’t count on the FDA to move a high-spend drug like Claritin® to the OTC shelf every year. Nor can you expect medical research to disprove the health benefits of a particular therapy like HRT. However, you always have the ability to influence participant behavior and provide the support to help participants to become better consumers and make the best use of their pharmacy benefit. Start now to examine strategies to manage utilization and trend in 2005.

**Figure 7**

Increasing utilization of mail yields greater drug list compliance and generic substitution, helping to lower trend. Retail refill restrictions and appropriate co-pay structures help drive mail utilization.

As a plan sponsor, you know that you can’t count on the FDA to move a high-spend drug like Claritin® to the OTC shelf every year. Nor can you expect medical research to disprove the health benefits of a particular therapy like HRT. However, you always have the ability to influence participant behavior and provide the support to help participants to become better consumers and make the best use of their pharmacy benefit. Start now to examine strategies to manage utilization and trend in 2005.
As a driver of trend in 2003, average wholesale price (AWP) increases accounted for just 3.5% of our Book of Business total 9.3%. As can be seen in figure 8, this is much closer to the historical norm than the abnormally large increases in 2002. Price increases accounted for 5.9% of our 2002 Book of Business trend of 13.9% (see figure 2). Facing patent expiration, for example, the manufacturer raised the price of Claritin® by more than 20% in 2002. In contrast, in 2003, the largest price increase among our top 25 drugs was just over 14%, for antidepressant Effexor®. The increase for Effexor®—which may go off patent in the months ahead—helped the manufacturer offset losses related to declining sales for estrogen products, a major product for the firm. Consistent with previous years, increases for brand drugs outstripped those for generics.

Figure 8
In 2002, average wholesale price (AWP) increases were abnormally high. In 2003, they fell back to more normal levels.
Product, It’s All in the Mix

In considering the impact of product on trend, we look at two factors: the impact of new drugs—both brands and biotechs—and the mix of drugs, that is the proportions of brands, generics and biotechs being used. Product was the highest driver of trend in 2003, at 4.2%. The major factors affecting product were: a continuing shift away from older drugs to newer drugs, an increased use of biologic therapies related to new biotech entrants, and new indications for existing products.

No new blockbuster brands. New entrants in the brand marketplace didn’t have a huge impact in 2003, accounting for just 0.8% of trend. Despite expectations, new cholesterol treatment Crestor®, which became available in September, achieved less than 1.4% market share by year’s end. Levitra®, a second erectile dysfunction (ED) drug, entered the market in August and earned less than a 7% share of the ED market. The numbers suggest that Levitra® and Cialis®, another ED drug approved late in the year, are expanding the market through new prescriptions. All three of these products are expected to increase their market share over time and possibly achieve blockbuster status.

Manufacturers put considerable marketing power behind these new entrants, yet their performance was disappointing. In the Caremark Book of Business, plan design strategy recommendations such as therapy protocols and quantity limits helped to blunt the impact of these and other new drugs.

Biotech introductions offer breakthroughs. The FDA approved close to 20 biologic products in 2003. Several of these new introductions target rare diseases for which there was previously no effective treatment or are indicated for cancers that have not responded to other treatments. Generally, these and other biotech products offer an entirely new mode of action by targeting specific types of cells involved in the disease process, thus promising better outcomes and potentially fewer side effects.

In 2003, for the first time, biologic products for high-incidence conditions—such as asthma and rheumatoid arthritis—gained FDA approval. Two biologic therapies were approved for psoriasis, potentially transforming the dermatologic category. In addition, some existing biotech therapies were approved for new indications, widening the market for their use.
Biotech trend and spend continue to increase in the Caremark Book of Business. Biotech products are entering the market at a record pace, and the biotech pipeline is increasingly weighted to therapies for high-incidence conditions. This market segment will assume ever-greater importance in benefit plan strategies.
## Major Drug Approvals in 2003

<table>
<thead>
<tr>
<th>Drug</th>
<th>Specialty/Biotech</th>
<th>Indication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advate</td>
<td>✘</td>
<td>hemophilia</td>
<td>Indicated for bleeding episodes; lowers risk of infection</td>
</tr>
<tr>
<td>Aldurazyme®</td>
<td>✘</td>
<td>enzyme deficiency</td>
<td>First treatment for rare genetic disorder</td>
</tr>
<tr>
<td>Amevive®</td>
<td>✘</td>
<td>psoriasis</td>
<td>First biologic approved for psoriasis</td>
</tr>
<tr>
<td>Aralast™</td>
<td>✘</td>
<td>enzyme deficiency</td>
<td>Rare disorder</td>
</tr>
<tr>
<td>Bexxar®</td>
<td>✘</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>For patients who have not responded to other treatments</td>
</tr>
<tr>
<td>Cialis®</td>
<td>✘</td>
<td>erectile dysfunction (ED)</td>
<td>Said to provide quicker onset of action and last longer than Viagra®</td>
</tr>
<tr>
<td>Crestor®</td>
<td>✘</td>
<td>high cholesterol</td>
<td>Said to be more effective than other statins, expected to gain considerable market share over time</td>
</tr>
<tr>
<td>Fabrazyme®</td>
<td>✘</td>
<td>Fabry’s disease</td>
<td>First treatment for rare and potentially fatal disorder</td>
</tr>
<tr>
<td>Flumist™</td>
<td>✘</td>
<td>flu vaccine</td>
<td>First intranasal vaccine, indicated for healthy people</td>
</tr>
<tr>
<td>Fuzeon™</td>
<td>✘</td>
<td>advanced HIV</td>
<td>New class of drugs for HIV</td>
</tr>
<tr>
<td>Iressa®</td>
<td>✘</td>
<td>advanced lung cancer</td>
<td>New mode of action for cancer treatment</td>
</tr>
<tr>
<td>Levitra®</td>
<td>✘</td>
<td>erectile dysfunction (ED)</td>
<td>By the end of 2003, men had a choice of three options for ED; wider choice expected to expand market for the category</td>
</tr>
<tr>
<td>Lexiva™</td>
<td>✘</td>
<td>HIV infection</td>
<td>For combination therapy</td>
</tr>
<tr>
<td>Namenda™</td>
<td>✘</td>
<td>Alzheimer's disease</td>
<td>New mode of action may slow the course of the disease</td>
</tr>
<tr>
<td>Raptiva®</td>
<td>✘</td>
<td>psoriasis</td>
<td>Unlike Amevive®, can be self-administered</td>
</tr>
<tr>
<td>Restasis®</td>
<td>✘</td>
<td>dry eye disease</td>
<td>Increases tearing</td>
</tr>
<tr>
<td>Reyataz™</td>
<td>✘</td>
<td>HIV/AIDS</td>
<td>For combination therapy</td>
</tr>
<tr>
<td>Seasonale®</td>
<td>✘</td>
<td>contraception</td>
<td>Extended cycle contraceptive, reduces user’s menstrual periods to four a year</td>
</tr>
<tr>
<td>Somavert®</td>
<td>✘</td>
<td>growth hormone</td>
<td>For treatment of acromegaly, a serious life-shortening disease</td>
</tr>
<tr>
<td>Symbyax™</td>
<td>✘</td>
<td>bipolar depression</td>
<td>First drug approved for bipolar depression, Symbyax™ combines Prozac®, an antidepressant and Zyprexa®, an antipsychotic</td>
</tr>
<tr>
<td>Velcade™</td>
<td>✘</td>
<td>cancer</td>
<td>For multiple myeloma patients who have not responded to previous treatment</td>
</tr>
<tr>
<td>Vigamox™</td>
<td>✘</td>
<td>eye infections</td>
<td>Easier dosing schedule</td>
</tr>
<tr>
<td>Xolair®</td>
<td>✘</td>
<td>asthma</td>
<td>For moderate to severe allergic asthma inadequately controlled by first-line treatments</td>
</tr>
<tr>
<td>Zymar™</td>
<td>✘</td>
<td>eye infections</td>
<td>New method of action</td>
</tr>
</tbody>
</table>
### Caremark Top 5 Therapeutic Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>What you should know</th>
<th>What to expect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol-lowering drugs—dominated by statins</td>
<td>The statins Lipitor® and Zocor® are the top-selling drugs in America. Several large studies have confirmed that statins reduce the risk of death or cardiovascular events. Research suggests that the 11 million people now taking statins are only a fraction of those who should be on the therapy, and many, particularly high-risk patients, should aim for lower LDL levels than previously recommended.</td>
<td>This huge market could expand further. Crestor®, launched in 2003, and a Zetia®-Zocor® combination, with expected launch in 2004, may potentially provide some market competition among the branded statins. Recent research indicates that high-risk patients on highly potent statins (e.g., Lipitor®) suffered fewer deaths and major cardiovascular problems—these findings are likely to spur further migration to the more potent statins.</td>
</tr>
<tr>
<td>Anti-ulcer drugs—dominated by proton pump inhibitors (PPIs)</td>
<td>Prescription Prilosec™—which is now also available OTC and as a generic—is no longer in the top ten. Prevacid® and Nexium® are among the top drugs in the U.S.</td>
<td>Prilosec™ OTC helped to moderate trend in this category, but did not bring about the major shifts that Claritin® OTC precipitated. The category is expected to hold steady.</td>
</tr>
<tr>
<td>Antidepressants—dominated by selective serotonin reuptake inhibitors (SSRIs)</td>
<td>Paxil®, Remeron®, Serzone®, and Wellbutrin® SR came off patent, while other SSRIs received expanded indications, for additional conditions including premenstrual syndrome, social anxiety disorder, and combination treatment for manic episodes associated with bipolar disorder.</td>
<td>Effexor® and Celexa® are expected to come off patent in 2004. Expect a shift to once-a-day Wellbutrin® XL.</td>
</tr>
<tr>
<td>Antihypertensives—includes ARBs, ACE inhibitors, diuretics, and calcium channel blockers</td>
<td>Several studies have concluded that thiazide diuretics, widely available as generics, should be first-line therapy for uncomplicated hypertension, but prescribing patterns have not shifted significantly to this less-expensive therapy.</td>
<td>An aging population and epidemic of obesity suggest continued increase in the incidence of hypertension. Ongoing publication of research results may result in moderate increase in antihypertensive utilization.</td>
</tr>
<tr>
<td>Anti-inflammatories—dominated by COX-2 inhibitors</td>
<td>Additional indications are being sought for several COX-2 inhibitors, which have been used primarily to treat symptoms of arthritis.</td>
<td>Additional indications and aging population could increase prescription rates for these drugs.</td>
</tr>
</tbody>
</table>

Source: Caremark Analytics & Outcomes, Book of Business Data

**Table 2**
Generics, Now More than Ever. New brand and biotech drugs are likely to increase your spend; generics are a prime strategy to reduce it. Generics introduced over the last three years, for example, reduced spend in the 2003 Caremark Book of Business by 3.1%. Many plan sponsors incentivized generics through co-pay structure and implemented other programs to support the utilization of generics. In addition, the U.S. consumer was exposed to widespread education about generics in 2003, much of it from pharmacy benefit managers like Caremark, but also from insurers, health organizations, the media, government groups, and the FDA. To some degree, these efforts paid off. Generic utilization rose in the Caremark Book of Business, and in the nation as a whole.

### Additional Key Category Changes

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Antibiotic utilization is expected to continue to decline; a recent study demonstrated that delaying a prescription for an antibiotic for pediatric ear infections helped to reduce inappropriate utilization.</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Explosive growth in utilization of the newer anticonvulsants may be due to off-label use to treat conditions such as neuropathic pain, migraines, obesity and bipolar disorder.</td>
</tr>
<tr>
<td>Behavioral Health</td>
<td>Abilify®, a new antipsychotic, and Strattera®, the first non-stimulant treatment for Attention Deficit Hyperactivity Disorder, were approved in late 2002.</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Biologic therapies Amevive® and Raptiva® were approved for plaque psoriasis. Approval for Enbrel® (see below) and other biologic therapies for this disorder is expected to follow this year, with anticipated unprecedented spending in the dermatologic category.</td>
</tr>
<tr>
<td>HIV Infection</td>
<td>The FDA approved five medicines for HIV infection, including Fuzeon™, a biologic therapy.</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Biotech therapy Humira™ was launched in 2003; Enbrel®, an injectable biologic drug received expanded indications and is expected to win approval for treatment of psoriasis this year, increasing its utilization.</td>
</tr>
</tbody>
</table>

Table 3
## Higher Utilization of Generics in 2003

<table>
<thead>
<tr>
<th>GSR</th>
<th>GSR</th>
<th>GDR</th>
<th>GDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>2003</td>
<td>2002</td>
<td>2003</td>
</tr>
<tr>
<td>94.3%</td>
<td>94.8%</td>
<td>40.8%</td>
<td>43.7%</td>
</tr>
</tbody>
</table>

### Impact of Recent Generic Introductions* on Spend in the Caremark Book of Business 2003: – 3.1%

To maximize utilization of cost-effective generics in your participant population, it’s important to have an appropriate spread between co-pays for brand and generic drugs. Education on generic availability and costs—through tools such as the Caremark iBenefit™ Report and Caremark.com—and on the safety and efficacy of generics—through our Count on Generics™ program—is also effective. Caremark has many additional strategies that help to increase utilization of generics including DAW programs and CustomCare Mail and Retail.

*Top 5 generic introductions for the years 2001–2003

GSR: Generic Substitution Rate, the number of generics dispensed for brands that have a generic available.

GDR: Generic Dispensing Rate, the total number of generics dispensed compared to all prescriptions dispensed.

Source: Caremark Analytics & Outcomes, Book of Business Data

### Table 4

In an effort to cut prescription drug costs, the FDA has pledged to expedite the approval of generics, a commitment that was reinforced in the Medicare reform bill approved in late 2003. The FDA goal for an expedited approval is 15 to 16 months. While each generic introduction offers potential savings, the particulars of each launch differ. In the case of omeprazole—generic for Prilosec™, the blockbuster proton pump inhibitor—limited supplies of the generic product delayed savings.

### Top Generic Introductions 2003

<table>
<thead>
<tr>
<th>Brand Drug Name</th>
<th>Generic Drug Name</th>
<th>Gross Cost/Day Generic</th>
<th>Gross Cost/Day Brand</th>
<th>Savings</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucophage® XR</td>
<td>metformin ER</td>
<td>$0.98</td>
<td>$1.66</td>
<td>41%</td>
<td>diabetes</td>
</tr>
<tr>
<td>Glucotrol® XL</td>
<td>glipizide ER</td>
<td>$0.49</td>
<td>$0.81</td>
<td>39%</td>
<td>diabetes</td>
</tr>
<tr>
<td>Paxil®</td>
<td>paroxetine</td>
<td>$1.85</td>
<td>$2.60</td>
<td>29%</td>
<td>depression</td>
</tr>
<tr>
<td>Prilosec™*</td>
<td>omeprazole*</td>
<td>$3.16</td>
<td>$4.13</td>
<td>23%</td>
<td>gastroesophageal reflux disease; ulcers</td>
</tr>
<tr>
<td>Remeron®</td>
<td>mirtazapine</td>
<td>$1.78</td>
<td>$2.78</td>
<td>36%</td>
<td>depression</td>
</tr>
<tr>
<td>Serzone®</td>
<td>nefazodone</td>
<td>$1.87</td>
<td>$2.98</td>
<td>37%</td>
<td>depression</td>
</tr>
</tbody>
</table>


Source: Caremark Analytics & Outcomes, Book of Business Data 2003

### Table 5

*Note: Generic forms of antihypertensive Monopril® and oral contraceptive Ortho Tri-Cyclen® were launched in late 2003.*
Paxil® became available as a generic product in September of 2003. The generic paroxetine is 30% cheaper than the brand Paxil®.

Over-the-counter drugs, a new factor in the equation. As discussed earlier, Claritin® OTC had a significant effect on trend in 2003 by diverting prescription users from the pharmacy counter to the drugstore aisle. Prilosec™ OTC, with more restrictive labeling and fewer dosage forms, had less impact although it did help to moderate growth of the proton pump inhibitor (PPI) category. The generic omeprazole will not be available over-the-counter for several years; until then, the category is expected to hold steady.

As another way to lower drug spend, the FDA is considering moving more brand big-sellers to the OTC shelf. Currently, discussion focuses on allergy products Allegra® and Zyrtec® and the cholesterol-reducing statins—some of the most frequently prescribed drugs in the United States. As with Claritin® and Prilosec™, the potential impact of such moves depends greatly on FDA-mandated labeling and indications.

Drug trend is a complex challenge. As a company focused on trend management, we at Caremark recognize that no single strategy is likely to achieve all your goals. That’s all the more reason to look ahead and keep an eye on the issues likely to affect your drug spend while employing proven management strategies:

- Encouraging use of the most cost-effective delivery system, our mail service pharmacies;
- Educating and empowering participants to choose low-cost products—generics and preferred drugs;
- Engaging participants to maximize utilization of these trend management tools and to support healthy behaviors.
Pharmaceutical Forecast

More than half of the top drug introductions in 2003 were biologic therapies or specialty pharmacy products (see table 1). For several years now, products in the biotech pipeline have been moving closer to center stage, capturing the attention and generating the excitement long accorded to brand introductions. 2004 will continue this trend. The long-term biotech pipeline is filled with hundreds of products with breakthrough potential, many of them targeting high-incidence conditions and/or diseases that currently have no effective treatment, including lupus and non-responsive cancers. The Medicare reform bill, which provides 100% coverage of drug costs over $5,200 for enrollees, could be a boost for some biotech products, such as those for rheumatoid arthritis and cancer. Biotechs will inevitably figure more and more in your drug spend. For many of these products, annual cost of treatment is $7,500 and more. The increasing number and utilization of these therapies underscores the need for a biotech plan of action for every plan sponsor.

Traditional brand manufacturers had a challenging year in 2003, and forecasts for 2004 are mixed at best. Despite expectations, no 2003 launch rose to blockbuster status. The hormone replacement therapy research, including additional publications from the Women’s Health Initiative (WHI), and Claritin’s move to over-the-counter substantially cut into industry sales. Furthermore, there is little excitement around the next group of anticipated launches. New combination products—such as Caduet® which combines cholesterol drug Lipitor® and antihypertensive Norvasc®, or Symbyax™, which combines Zyprexa®, an antipsychotic, with Prozac®, the antidepressant—are one strategy to compensate for temporarily dry pipelines. Applying for new indications for existing products is another. Early 2004 reports indicate that AWP increases are tracking higher than those for 2003 (see figure 11).

Figure 11

Q1 2004 AWP increases are higher than those in 2003.

AWP increases will likely play a larger role in trend in 2004 than in 2003.
Meanwhile, generics and over-the-counter drugs, with the FDA’s support, are expected to continue to gain ground. Medicare discount cards are scheduled to be launched the first half of 2004 as an interim measure until the full drug benefit is implemented in 2006. They’ll provide some assistance with prescription prices for seniors that currently have no drug coverage and could thereby increase the market and utilization of drugs across the country.

**2004 Anticipated Brand and Biotech Launches**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Biotech/ Specialty</th>
<th>Indication</th>
<th>Est. U.S. Sales (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimta®</td>
<td>☒</td>
<td>cancer</td>
<td>$500-$999</td>
</tr>
<tr>
<td>Arcoxia®</td>
<td>☒</td>
<td>osteoporosis/rheumatoid arthritis</td>
<td>&gt;$1000</td>
</tr>
<tr>
<td>Avastin™*</td>
<td>☒</td>
<td>cancer</td>
<td>N/A</td>
</tr>
<tr>
<td>Caduet™**</td>
<td>☒</td>
<td>cardiovascular disease</td>
<td>N/A</td>
</tr>
<tr>
<td>Cymbalta™</td>
<td>☒</td>
<td>depression</td>
<td>&gt;$1000</td>
</tr>
<tr>
<td>Erbitux™*</td>
<td>☒</td>
<td>cancer</td>
<td>N/A</td>
</tr>
<tr>
<td>Exanta™</td>
<td>☒</td>
<td>prevention and treatment of blood clots</td>
<td>N/A</td>
</tr>
<tr>
<td>Inspra™*</td>
<td>☒</td>
<td>hypertension, congestive heart failure</td>
<td>N/A</td>
</tr>
<tr>
<td>Ketek</td>
<td>☒</td>
<td>infectious disease</td>
<td>&gt;$1000</td>
</tr>
<tr>
<td>Spiriva®*</td>
<td>☒</td>
<td>asthma/chronic obstructive pulmonary disease (COPD)</td>
<td>&gt;$1000</td>
</tr>
<tr>
<td>Vytorin™**</td>
<td>☒</td>
<td>high cholesterol</td>
<td>&gt;$1000</td>
</tr>
</tbody>
</table>

*Approved early 2004.
**Probable name for Zetia/Zocor combination

The timing of new drug approvals is dependent on the FDA.

**Table 6**

**New Products to Watch**

- Exanta®, the first new anticoagulant in 50 years, is said to be as effective, faster acting, and to present fewer problematic interactions than warfarin
- Inspra™, indicated for post-heart attack patients, is expected to improve survival rates and reduce the need for defibrillators
- Spiriva®, the first once-daily inhaled bronchodilator for chronic obstructive pulmonary disease
- Arcoxia®, a new COX-2 inhibitor like Celebrex® and Vioxx®, used to treat arthritis
The first biologic therapies are coming of age and will be losing their patent protection over the next several years. However, many questions remain about approval processes, assuring bioequivalency, and replicating highly sensitive manufacturing processes. The FDA is taking the first steps toward establishing procedures and guidelines, and generic biologic therapies are considered inevitable—but not in the near future. When they are finally available, don’t count on them to offer the level of savings you’ve come to expect from other generics.

The most effective strategy to manage biotech costs continues to be care management through programs such as Caremark BioCare Solutions℠. Biocare Solutions℠ provides total chronic care management for each participant on such therapy, with the goals of improving clinical outcomes and controlling costs.

### Anticipated Generic Launches 2004

<table>
<thead>
<tr>
<th>Indication</th>
<th>Brand</th>
<th>U.S. Sales (M)</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>attention deficit/hyperactivity disorder (ADHD)</td>
<td>Concerta®</td>
<td>$500</td>
<td>methylphenidate HCI</td>
</tr>
<tr>
<td>convulsive disorders</td>
<td>Neurontin®</td>
<td>$2,269</td>
<td>gabapentin estradiol</td>
</tr>
<tr>
<td>depression</td>
<td>Wellbutrin® SR</td>
<td>$1,500</td>
<td>bupropion</td>
</tr>
<tr>
<td>diabetes</td>
<td>Glucovance®</td>
<td>$500</td>
<td>glyburide, metformin</td>
</tr>
<tr>
<td>hypertension</td>
<td>Lotensin**</td>
<td>$333</td>
<td>benazepril HCl</td>
</tr>
<tr>
<td>infection</td>
<td>Cipro®</td>
<td>$1,600</td>
<td>ciprofloxacin</td>
</tr>
<tr>
<td>fungal infection</td>
<td>Diflucan®</td>
<td>$1,112</td>
<td>fluconazole estradiol</td>
</tr>
<tr>
<td>hepatitis C</td>
<td>Rebetol®</td>
<td>$865</td>
<td>ribavirin</td>
</tr>
<tr>
<td>pain</td>
<td>Oxycontin®</td>
<td>$1,200</td>
<td>oxycodone</td>
</tr>
</tbody>
</table>

All projected launch dates are estimates. Caremark actively monitors the progress of generic availability and will provide ongoing updates as additional information becomes available.

### Table 7

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<td>gabapentin estradiol</td>
</tr>
<tr>
<td>DEPRESSION</td>
<td>Wellbutrin® SR</td>
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<td>bupropion</td>
</tr>
<tr>
<td>DIABETES</td>
<td>Glucovance®</td>
<td>$500</td>
<td>glyburide, metformin</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>Lotensin**</td>
<td>$333</td>
<td>benazepril HCl</td>
</tr>
<tr>
<td>INFECTION</td>
<td>Cipro®</td>
<td>$1,600</td>
<td>ciprofloxacin</td>
</tr>
<tr>
<td>FUNGAL INFECTION</td>
<td>Diflucan®</td>
<td>$1,112</td>
<td>fluconazole estradiol</td>
</tr>
<tr>
<td>HEPATITIS C</td>
<td>Rebetol®</td>
<td>$865</td>
<td>ribavirin</td>
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The most effective strategy to manage biotech costs continues to be care management through programs such as Caremark BioCare Solutions℠. Biocare Solutions℠ provides total chronic care management for each participant on such therapy, with the goals of improving clinical outcomes and controlling costs.

### The influence of politics in 2004

- Pending implementation of portions of the Medicare reform bill could increase the market for prescription drugs and help to moderate price increases.

- Consumers and state and municipal governments continue to advocate the reimportation of drugs. Former FDA head Mark McClellan has been given responsibility for investigating the safety of reimported drugs. Movement on reimportation—in either direction—is sure to change the dynamics of the market.

- The FDA has indicated continuing interest in expediting the approval of generics and approving more brand drugs for OTC sale. The agency is also considering loosening restrictions on pharmaceutical advertising—a move that will impact brand drug manufacturers, who invest more in advertising.

- If the Democratic challenger takes the White House in the upcoming Presidential election, expect changes in healthcare policies. Probable areas of contention include implementation of the Medicare reform bill and drug re-importation.
How will Consumer-Directed Plans perform?

More employers offered consumer-directed health (CDH) plans for 2004 than 2003, and more employees chose them. An estimated one million employees were enrolled in CDH plans as of January 1, 2004. A larger population in CDH plans should translate into better data to evaluate the effectiveness of this strategy in controlling costs.

Initial evaluations of populations choosing CDH plans suggest that concerns about adverse selection are valid. A risk in offering these plans is that healthier, lower-cost individuals will choose to enroll in the CDH option, leaving higher-cost participants in more traditional plans, a situation analysts have defined as “adverse selection.” In adverse selection, risk is no longer shared across the entire participant pool, but concentrated in the traditional plan, leading to higher premiums. Thus, while the CDH plan may appear to reduce costs and utilization, the lower spending levels are actually due to a healthier, less costly pool of enrollees.

Watch TrendsRx Quarterly and the TrendsRx 2004 Series for further analysis of CDH performance. To support your consumerist goals, ask your Caremark account representative about our continuum of plan design solutions and clinical programs that will expose participants to drug costs and help educate and encourage them to make wiser healthcare decisions.

Trend Management Strategies in 2004
Changes in pharmacy benefit plans tend to be cyclical in nature; a year of aggressive change, such as 2003, is followed by a year in which plan sponsors make fewer and potentially less disruptive changes. 2004 is consistent with this pattern. This year, employers are embracing aspects of a consumerist philosophy, but implementing fewer cost share adjustments and plan design changes. The number of Caremark clients with three-tier co-pay structures continues to increase, and more DAW (dispense as written) programs are being implemented (see figure 12). Both of these strategies aim to influence participants to make cost-effective prescription choices.

Caremark clients also hope to engage and educate participants to encourage healthy decisions through clinical pharmacy programs. Many recognize the value of disease management programs, which are a natural complement to consumerist strategies as they support the participant in compliance with recommended therapies, thereby helping to contain medical claims.
Based on this pattern of plan structures, we expect pharmacy benefit trend for 2004 to be in the 13 to 15% range. To help control your pharmacy benefit trend, Caremark recommends strategies that:

- Increase participants’ price awareness
- Reinforce the value of generics as alternatives to brand drugs
- Encourage the use of mail service over retail for long-term maintenance medications

Figure 12

DAW (dispense as written) penalty programs support the use of lower-cost generic drugs. These programs require that participants pay a penalty for choosing a brand-name drug when a generic is available. Under DAW-A programs, there is no penalty if the physician specifies the brand-name drug; under the more restrictive DAW-B program, there is a penalty regardless of who—physician or participant—chooses the brand-name drug. Caremark is recommending the more restrictive program, and clients are opting for it in increasing numbers.
TrendsRx® 2004 Series

Analysis and Insights for Optimizing Your Healthcare Investment
To help you negotiate the challenges of 2004, Caremark has developed the new TrendsRx® 2004 Series to provide timely news, information and analyses.

With the TrendsRx® 2004 Series and Web site www.trendsrxseries.caremark.com, we’re adding another dimension to the consultative support you receive from Caremark. Your pharmacy benefit is an investment—affecting participant health and satisfaction as well as productivity and the bottom line. With a focus on trend management, it is our commitment to guide you throughout the year in developing a pharmacy benefit plan that meets your organization’s near- and long-term goals for the physical and financial health of your organization.

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✔ Pharmaceutical pipeline reports
✔ Pharmacy benefit planning support
✔ Comprehensive information on Caremark Trend Management tools
✔ Case studies
✔ Benchmarking
✔ In-depth guide to Total Healthcare Management programs, including participant engagement strategies
✔ Timely reports on research and top issues in healthcare

Please visit www.trendsrxseries.caremark.com to learn more about TrendsRx® tools and Caremark programs and resources.
Sources


4. Top Five Benefit Priorities


6. Employer Health Benefits


10. Inside Consumer Directed Care, October 31, 2003

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These figures and tables are available for downloading at www.trendsrxseries.caremark.com

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**Note:** In this book we talk about co-payment. Co-payment or co-pay means the amount a participant is required to pay for prescription in accordance with a Plan, which may be a deductible, a percentage of the prescription price, a fixed amount or other charge, with the balance, if any, paid by the Plan.
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