DRUG TREND 2002 Report

june 2003

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The Bottom Line

Per Member Per Year (PMPY) ingredient costs continued to rise, increasing by 18.5 percent in 2002. It is projected that PMPY drug costs will increase by 107 percent over the next five years.

Acknowledgements: The authors owe special thanks to the following people who provided substantial input and comments: Brian Ellis, BS; Raulo Frear, PharmD; Craig Kephart, RRT; Brenda Motheral, PhD and Suzanne Vargas, BS.

2002 Express Scripts Drug Trend Report

June 2003

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Preface

Dear Reader,

Prescription drugs are used by more Americans as first-line treatments for an increasing number of diseases. In turn, as we use more drugs to treat diseases, the total cost of the prescription drug benefit grows.

This year, Express Scripts' *Drug Trend Report* summarizes the factors that are driving up the cost of prescription drug benefits and in doing so identifies several important findings:

- Generic drugs are quickly gaining market share. The generic fill rate reached 45.9 percent in the fourth quarter of 2002, and the use of generic drugs is expected to climb to more than 50 percent by 2004, if not sooner.
- Specialty drugs — primarily biotech drugs that require special handling — make up an ever-growing percentage of the prescription drug bill (including drug costs incorporated into the medical line item). Mainly used to treat rare diseases, specialty drug use is likely to rise at a rapid rate.
- Overall, prescription drug costs continue to grow at a double-digit rate, due in part to rising utilization.

Express Scripts is committed to helping plan sponsors provide prescription drugs to their employees/members. Last year, Express Scripts assisted our clients in lowering the cost of prescription drugs by 30 percent as compared to full retail price. We made prescription drugs more affordable by increasing the use of:

- Generics
- Mail service
- Low-cost formulary brand drugs

While lowering cost, we also helped to make the use of prescription drugs safer by sending out over 33 million safety warnings that resulted in almost 500,000 changes to drug therapy.

Not only has Express Scripts expanded the explanation of the pharmacy benefit in this year's *Drug Trend Report,* we have also broadened our services to make prescription drug use safer and more affordable.

Sincerely,

Barrett A. Toan
Chairman and Chief Executive Officer

Introduction

Background

The year 2002 was a year characterized by national concern over homeland security, the war on terrorism, potential war with Iraq, a sluggish economy, and federal and state surpluses that turned into substantial deficits. In the public sector, the addition of a Medicare prescription drug benefit died over philosophical and partisan differences. Proposals for a Medicare prescription drug benefit have reappeared, but they are embroiled in debates over comprehensive Medicare reform. In addition, they must somehow be financed as budget deficits continue to grow. Unlike the federal government, states are required to have balanced budgets. In 2002, most states experienced severe budget problems that continue into 2003 and likely into 2004. As a consequence, many states have been forced to reduce spending for Medicaid, the federal/state program that provides medical care for the poor. Budget problems were not limited to the public sector, however. The economic downturn hit the private sector hard, resulting in large layoffs and subsequent rises in unemployment rates, as well as in a growing inability of employers to pay for the rapid growth in healthcare premiums.

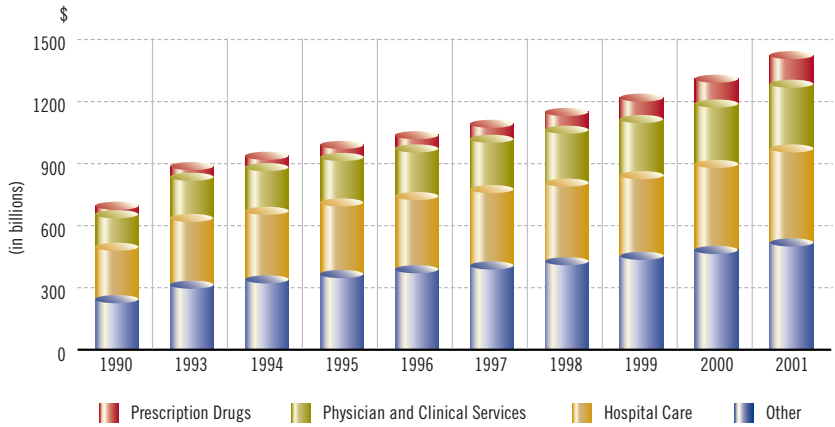
As economic problems hurt the public and private sectors, healthcare costs increased substantially. After stabilizing at between 5 percent and 6 percent between 1994 and 1998, the annual growth rate in total national health expenditures has inched up, reaching $1.4 trillion, or $5,035 per capita, in 2001 — 8.7 percent above 2000 levels[1] (see Figure 1). National health expenditures for prescription drugs grew at an even more sizeable annual rate, peaking at 19.7 percent in 1999 before ebbing to still significant annual growth rates of 16.4 percent and 15.7 percent in 2000 and 2001, respectively. These rates of increase were higher than any of the other major components of national health expenditures.

In contrast, the annual growth rate in national expenditures for hospital care and physician and clinical services rose over the last several years — particularly in 2001 — after declining in the early and mid-1990s. The annual growth of expenditures for hospital care actually declined from 10.1 percent in 1990 to 2.9 percent in 1998, before creeping back up to 8.3 percent in 2001. Annual growth rates in national spending for physician and clinical services declined from 11.2 percent in 1990 to 4 percent in 1996 before rising by 5 percent, 6.6 percent, 5.2 percent, 6.9 percent and 8.6 percent in the five succeeding years. As a proportion of overall national healthcare costs, prescription drugs rose from 5.8 percent in 1990 to 9.9 percent in 2001. Conversely, the percentage attributed to hospital care slowly declined from 36.5 percent in 1990 to 31.7 percent in 2001, while the proportion of total spending attributable to physician and clinical services remained stable at about 22 percent.

1 Adapted from: Centers for Medicare & Medicaid Services, Office of the Actuary: National Health Statistics Group; U.S. Department of Commerce, Bureau of Economic Analysis; and U.S. Bureau of the Census. Table 1: National Health Expenditures Aggregate and Per Capita Amounts, Percent Distribution, and Average Annual Percent Growth, by Source of Funds: Selected Calendar Years 1980-2001 and Table 2: National Health Expenditures Aggregate Amounts and Average Annual Percent Change, by Types of Expenditure: Selected Calendar Years 1980-2001. Available at: http://www.cms.hhs.gov/statistics/nhe/historical/tables.pdf. Accessed January 30, 2003.

Figure 1

National Health Expenditures for Selected Healthcare Accounts 1990 and 1993-2001



Source: Centers for Medicare & Medicaid Services, Office of the Actuary: National Health Statistics Group. Table 2: National Health Expenditures Aggregate Amounts and Average Annual Percent Change, by Types of Expenditure: Selected Calendar Years 1980-2001. Available at: http://www.cms.hhs.gov/statistics/nhe/historical/tables.pdf. Accessed January 30, 2003.

Although spending for prescription drugs has grown at a dramatic rate, the absolute dollar amount expended on prescription medicines is substantially below what is spent on hospital care and physician and clinical services. By 2001, per capita prescription expenditures totaled $497. By comparison, per capita spending for prescription drugs was less than one-third of what was expended for hospital care ($1,594) and less than one-half of the expenditure for physician and clinical services ($1,108).[2] Consequently, even though the percentage growth in per capita spending for prescription drugs between 2000 and 2001 was far higher than for hospital care and physician and clinical care, the absolute annual dollar increases for hospital care ($106) and physician and clinical care ($77) were larger than for prescription drugs ($63).[3]

The Office of the Actuary for the Centers for Medicare and Medicaid Services (CMS) projects that national health expenditures will grow by 8.6 percent in 2002, then gradually decline to an annual 6.9 percent growth rate in 2009 and remain at about that level through 2012. Expenditures for prescription drugs are predicted to grow by 14.3 percent in 2002, with the annual rate of growth declining to 9.5 percent from 2009 through 2012. As a result, the proportion of total national health expenditures accounted for by prescription drugs is projected to grow from 9.9 percent in 2001 to 14.5 percent in 2012.[4]

2 Levit K, Smith C, Cowan C, Lazenby H, Sensenig A, Catlin A. Trends in U.S. health care spending, 2001. *Health Affairs*. 2003;22(1):154-164.

3 ibid.

4 Centers for Medicare and Medicaid Services, Office of the Actuary; and the U.S. Department of Commerce, Bureau of Economic Analysis and Bureau of the Census, as cited in: Heffler S, Smith S, Keehan S, Clemens MK, Won G, Zezza M. Health care spending projections for 2002-2012. *Health Affairs-Web Exclusive*. No Date Given. Available at: http://www.healthaffairs.org/WebExclusives/2202Heffler.pdf. Accessed January 2003.

The impact of rising health costs has been felt by state Medicaid agencies, as well as by private employers. In terms of the former, total Medicaid costs grew by 13.4 percent in 2002, on top of the 11 percent growth experienced in 2001. They are expected to grow by about another 9 percent in 2003.[5] Prescription drug costs have been a major driver of these increases. Indeed, between 1998 and 2000, annual Medicaid prescription drug costs grew by around 20 percent and increased by over 28 percent in 2001.[6] While the increasing number of Medicaid recipients has contributed to this growth, the ascension of drug costs is explained only partially by this phenomenon. (See Appendix B for a more detailed explanation of Medicaid prescription cost trends.) In terms of the latter, private health benefit premiums have risen substantially over the last several years, and that increase is projected to continue into 2003. A Buck Consultants survey of health insurers found that health premiums grew between 13 percent and 14.9 percent in 2002. Depending on the product, the rate of growth was projected to continue at about those same levels in 2003. The trend for prescription drug card programs was 18.4 percent in 2002, and it is projected to be 16.9 percent in the first half of 2003.[7] The 2003 Segal Company Cost Trend Survey reported that 2003 medical plan costs, including prescription drugs, will rise between 14.4 percent and 16.2 percent, depending on plan type. Prescription drug carve-out plans are anticipated to grow by 19.5 percent in 2003 for those under 65 years old and by 19 percent for those 65 and older.[8] A poll conducted by Mercer Human Resource Consulting found that healthcare premiums will increase by 14 percent in 2003 after growing by 14.7 percent in 2002. Together, these growth rates represented the largest two-year increase since 1990.[9] Finally, Hewitt Associates reported that companies are anticipating a 15 percent rise in health premiums in 2003[10] while Towers Perrin reports expected increases of 16 percent.[11]

The figures cited above clearly demonstrate the magnitude of the financial burden that plan sponsors must bear for health benefit costs. Stories abound in the media regarding the negative effects that rising health premiums have on companies and on employees and their families. According to Hewitt, "The majority (94 percent) of participating companies also report that their CEO, CFO and CHRO are significantly or critically concerned about the rising costs of health benefits and the impact on corporate costs, while exactly 90 percent are significantly or critically concerned about their impact on employees."[12] Larger employers reduced the number of HMO plans they

5 Smith V, Ellis E, Gifford K, Ramesh R, Wachino V. Medicaid spending growth: a 50-state update for fiscal year 2003. Kaiser Commission on Medicaid and the Uninsured. January 2003. Available at: http://www.kff.org/content/2003/20030113/4082.pdf. Accessed January 14, 2003.

6 Adapted from: Medicaid Statistical Information System (MSIS) and HCFA-2082 State tables. Available at: http://cms.hhs.gov/medicaid/msis/mstats.asp. Accessed September 24 and 27, 2002, and October 2 and 16, 2002.

7 Health care costs continue to rise, according to survey by Buck Consultants [press release]. New York: Buck Consultants; August 8, 2002. Available at:http://www.buckconsultants.com/content/pr293.html. Accessed March 25, 2003.

8 2003 Segal Health Plan Cost Trend Survey [abstract]. November 2002. Available at: http://www.segalco.com/corporate/pub-corporate.cfm?ID=415. Accessed February 2, 2003.

9 Rate hikes pushed employers to drop health plans, cut benefits in 2002-but average cost still rose 14.7% [press release]. New York: Mercer Human Resource Consulting; December 9, 2002.

10 Employers concerned about the impact of rising health care costs and are evaluating alternatives [press release]. Lincolnshire, Illinois: Hewitt News and Information; January 14, 2003.

11 Enochs, L. Employment: rising health care costs impact hiring rates. *The Seattle Times*. February 13, 2003. Available at: http://archives.seattletimes.nwsource.com/cgi-bin/texis.cgi/web/vortex/display?slug=bizhealthcosts13&date=20030213&query= health+care+Enochs. Accessed February 14, 2003.

12 Employers concerned about the impact of rising health care costs and are evaluating alternatives [press release]. Lincolnshire, Illinois: Hewitt News and Information; January 14, 2003.

offered and used this added leverage, in conjunction with plan design changes, to curb HMO growth to 8.1 percent. In contrast, smaller employers, with no buying leverage, saw HMO premiums jump by 25.9 percent in 2002. Faced with such substantial increases in healthcare costs, the percentage of smaller employers — those with between 10 and 50 employees — that offered a health plan dropped from 66 percent to 62 percent.[13] Some companies that have declared bankruptcy have eliminated health benefits for retirees.[14] Most plan sponsors have and/or will raise members' financial responsibility for healthcare costs through higher member copayments/ deductibles or premium contributions. Some momentum is also building toward more consumer-driven approaches, such as tiered copayments for networks, drugs and consumer-directed health plans.[15,16] In a sign that employees are becoming increasingly concerned about their health benefits, General Electric Company's union workers threatened to strike over rises in healthcare copayments.[17]

While the overall picture of rising health and pharmacy costs appears bleak, the prescription drug side of the equation includes a couple of positive dynamics that may moderate the magnitude of future cost increases. First, several heavily used brand products — Prozac®, Glucophage®, Zestril®/Prinivil®, Zestoretic®/Prinzide® and Prilosec® — have lost patent protection, allowing generic versions to enter the market in the past 18 months. Prozac®, an antidepressant, went generic in August 2001 and within 12 weeks, about three-fourths of Prozac® prescriptions for Express Scripts members were converted to the generic (fluoxetine). The generic conversion rate (the proportion of multi-source brand prescriptions that have been filled by generics) for Prozac® has stabilized at about 94 percent. In 2002 the combined market share for Prozac® and fluoxetine actually declined from 14.8 percent in January to 13 percent in December. When the oral antidiabetic agent Glucophage® went generic in late January 2002, it experienced a rapid conversion from the brand to the generic product (metformin). Within 2 months, over 80 percent of branded Glucophage® was converted to metformin and over 90 percent within 6 months. The combined market share of Glucophage® and metformin declined slightly (1.4 percentage points) during 2002 (see Figure 2). The conversion of brand Zestril®/ Prinivil® and Zestoretic®/ Prinzide® to their respective generic equivalents was even faster, reaching 85 percent in 2 months and 90 percent in 4 months. Despite the relative therapeutic equivalency of other brand products in this therapeutic class, the combined market share of Zestril®/ Prinivil® and Zestoretic®/ Prinzide® and their respective generic equivalents remained flat at about 29 percent (see Figure 3).

13 Rate hikes pushed employers to drop health plans, cut benefits in 2002-but average cost still rose 14.7% [press release]. New York: Mercer Human Resource Consulting; December 9, 2002.

14 Caruso D. Sour economy, corporate scandals put retirees' health benefits in peril. *St. Louis Post Dispatch.* February 15, 2003.

15 Kaiser Family Foundation. National survey of small businesses. April 2002. Available at: http://www.kff.org/content/2002/20020402a/. Accessed January 2003.

16 Rate hikes pushed employers to drop health plans, cut benefits in 2002-but average cost still rose 14.7% [press release]. New York: Mercer Human Resource Consulting; December 9, 2002.

17 G.E. workers set to strike over insurance. *Bloomberg News.* December 31, 2002. Available at: http://coveringtheuninsured.org/news/index.php?NewsID=145. Accessed January 2003.

Figure 2
2002 Generic Conversion Rates for Glucophage® to Metformin and Market Share for Glucophage® and Metformin

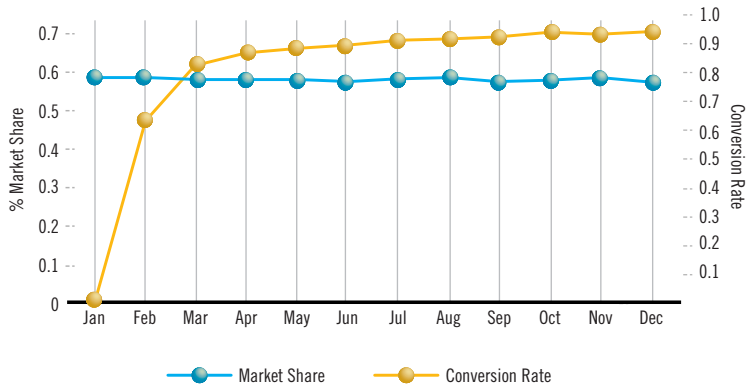
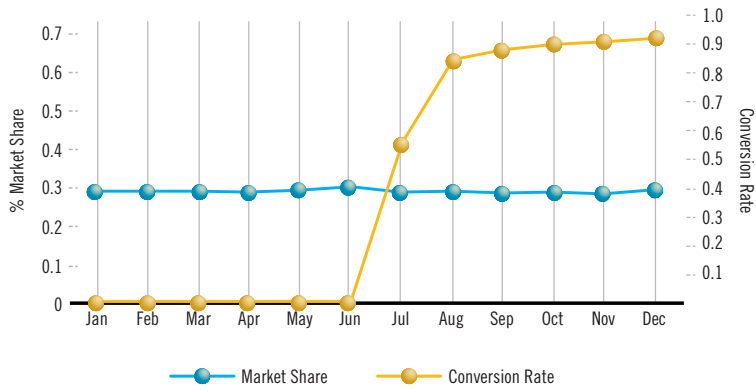


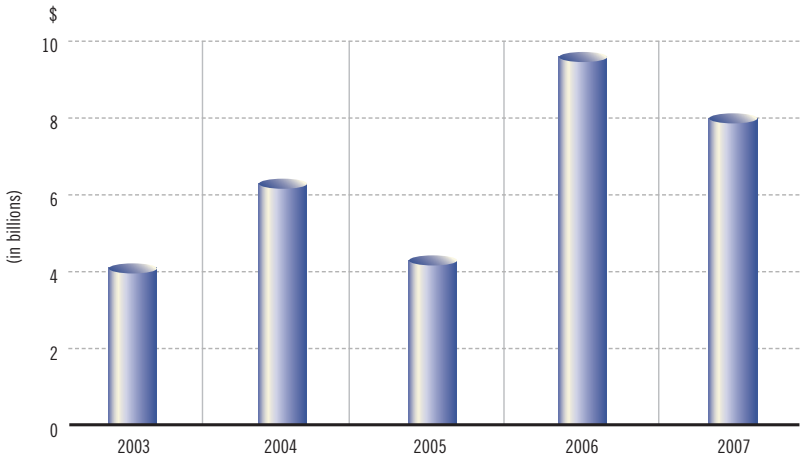
Figure 3
2002 Generic Conversion Rates for Zestril®/Prinivil® to Lisinopril and Prinzide®/Zestoretic® to Lisinopril/HCTZ and Market Share for Zestril®/Prinivil®, Prinzide®/Zestoretic®, Lisinopril and Lisinopril/HCTZ



A significant number of additional brands will lose their respective patents in the next several years. Indeed, as is shown in Figure 4, $32.3 billion worth of brand patents will expire over the next 5 years. These products represent 16.8 percent of U.S. prescription drug sales in 2002.[18] The impact on prescription drug costs, and consequently on trend, will be considerable. In 2002, the use of generic products instead of their branded counterparts reduced trend by 2.1 percent, or $12.70 Per Member Per Year (PMPY). The generic fill rate, which grew from 41.5 percent in the fourth quarter of 2001 to 45.9 percent in the fourth quarter of 2002, is projected to increase to 53.1 percent by the fourth quarter of 2007[19] (see Figure 5). Those percentages could increase even more, as would the reduction in trend, if the use of generic products went beyond mere substitution for their brand product counterparts and extended to utilization, when appropriate for a given patient, instead of other therapeutically equivalent brand products.

Figure 4

U.S. Sales for Brand Products with Patent Expirations Between 2003 and 2007



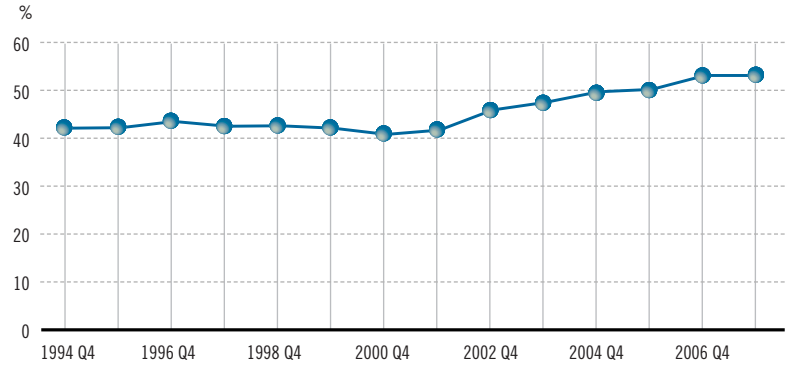
Adapted from: JP Morgan Securities, Inc. Industry update. *Prescription Pad*. February 14, 2003, and Marketos M. Top 200 brand and generic drugs by retail sales. *Drug Topics*. 2002;4:31 Available at: http://dt.pdr.net/be_core/content/journals/d/data/2002/0218/d0top200rxs02b.html. Accessed February 18, 2003.

18 Adapted from: IMS reports 11.8 percent dollar growth in 2002 U.S. prescription sales. [press release]. Plymouth Meeting, Pennsylvania: IMS Health; February 21, 2003. Available at: http://www.imshealth.com. Accessed February 21, 2003.

19 Express Scripts data and projections.

Figure 5

Generic Fill Rate Fourth Quarter 1994 to Fourth Quarter 2007 (Estimated)



Source: Express Scripts data and projections.

A second noteworthy event in 2002 was the introduction of prescription strength Claritin® (loratadine) to the over-the-counter (OTC) market. In the past, most OTC products were lower in strength than the prescription version of those products. In the case of Claritin®, however, the prescription strengths went OTC and the prescription versions were removed from the market. This action is consistent with current FDA regulations, which state that a drug product cannot exist as both a prescription and an OTC product in the same strength and for the same uses. Moreover, OTC Claritin was not brought to market until December 2002. Most plan sponsors had little or no time to determine whether to cover only OTC Claritin® (and now other OTC versions of loratadine) in 2003, and/or to cover some or all of the prescription non- and low-sedating brand antihistamine products and, if so, at what copayment levels. Nonetheless, the OTC availability of non-sedating antihistamine products represents a previously unavailable avenue for plan sponsors to use in reducing prescription drug costs by changing drug coverage rules and/or attaching high copayments to the prescription products.

Prilosec® potentially represents a hybrid opportunity for capitalizing on generic and OTC products to reduce costs — but with important caveats. First, as a result of a court decision, generic Prilosec® (omeprazole) in both the 10mg and 20mg strengths can be manufactured by only one company, and that exclusive right could last for months, if not years. This situation is unusual because the first generic manufacturer generally is granted exclusive marketing rights for only the first 6 months of generic availability. Therefore, the price of a newly-introduced generic product is typically higher than its price after the first 6 months when competitive pressures from multiple manufacturers drive down the price. Because of the extended exclusivity attached to omeprazole, its initial relatively high price could extend for up to 5 years until additional manufacturers can also bring omeprazole to market. Thus, when brand rebates are taken into account, the price difference between generic omeprazole and branded proton pump inhibitor (PPI) products is much less than usual. Moreover, even in the short run, the use of omeprazole has been curtailed by an insufficient supply of the product.

A second reason that the Prilosec®/omeprazole situation is unique relates to its OTC status. When labeling issues are finalized, the Food and Drug Administration (FDA) will grant the 20mg strength of Prilosec® OTC status; but only with a recommendation that its use be limited to 14 days, based on clinical reasons. Prescription Prilosec® has several long-term indications. The short-term use guidance for the OTC version puts plan sponsors in a difficult position when deciding whether to cover OTC Prilosec®, but not similar prescription proton pump inhibitors; to cover only the OTC product; to cover the OTC product at a relatively low copayment while covering prescription products at a substantial copayment; or to cover prescription PPIs only and forego the OTC opportunity.

Against this backdrop, prescription drug costs continue to increase substantially, and they are projected to grow at double digit rates for the foreseeable future. However, there are opportunities to reduce the rate of such increases, primarily through promoting the use of generic and lower cost brand products. The magnitude of trend increases in the future will reflect the degree to which plan sponsors are willing to adopt plan design strategies that encourage the use of these lower cost products.

Summary Of Findings

In 1997, Express Scripts published the first edition of the *Drug Trend Report* covering the 1993-1996 time period. The intent of the *Drug Trend Report* series is to provide our clients with a better understanding of the dynamics underlying both current drug cost increases and future drug cost trends. This seventh edition of Express Scripts' *Drug Trend Report* discusses the magnitude of and the reasons for prescription drug cost increases between 2001 and 2002. Among the key findings of this study are:

Between 2001 and 2002

- PMPY ingredient costs grew by $91.40, or 18.5 percent in 2002.
- The rise in per prescription costs accounted for 60.5 percent of this overall increase; 34.2 percent is attributable to increased utilization and 5.3 percent to the introduction of new drugs.
- The inflation rate for common drugs (drugs available in 2001 and 2002) grew by 7.5 percent — the fifth consecutive year that inflation topped 5 percent and the highest rate seen since the *Drug Trend Report* was initiated. Inflation accounted for 43.4 percent of the overall 2001-2002 drug expenditure increase.
- The use of generics instead of their respective brand counterparts reduced the PMPY ingredient cost increase by 2.1 percent.
- Slightly more of the utilization increase was due to more members using prescription drugs than to more prescriptions per utilizer.
- Ten drug classes accounted for 53.9 percent of the total 2002 PMPY ingredient cost.

- Higher costs of gastrointestinal, antihyperlipidemic, antidepressant and antihypertensive medicines accounted for $33.30, or 36.4 percent, of the total $91.40 PMPY ingredient cost increase in 2002.

- Five percent of members accounted for 50.7 percent of total 2002 PMPY ingredient cost and 10 percent of members for 69.7 percent of ingredient cost.

2003 Through 2007 Projections

PMPY ingredient costs are projected to increase by:

- 15.5 percent in 2003
- 16.0 percent in 2004
- 16.0 percent in 2005
- 15.6 percent in 2006
- 15.2 percent in 2007

These trend figures reflect past experience with and future expectations about the magnitude of drug cost increases on an ingredient cost basis. When considered from a net cost perspective — costs after member financial contribution and manufacturer rebates — plan sponsors can significantly curb costs. Plan sponsors that took aggressive steps saw their drug cost trend actually decrease by as much as 20 percent, with the average PMPY net claim cost increase being between 6 percent and 11 percent.

The key cost drivers that underlie the 2001-2002 drug cost growth are discussed in the first section of this Report. Express Scripts' forecast of PMPY ingredient costs for the period from 2003-2007 is then presented, along with a discussion of the new drug pipeline anticipated during this period. Also included in the forecast section is an analysis of the key products that are scheduled to lose patent protection between 2003 and 2007. A new chapter this year focuses on specialty injectable pharmacy products and the growing role these drugs have in the overall drug treatment arsenal. The concluding portion of this Report discusses the types of actions that plan sponsors can take to offset growing prescription costs. Appendix A includes an analysis of drug cost changes within the most costly therapy classes between 1998 and 2002. Also highlighted are some of the key changes in utilization of specific drugs and drug classes, as well as factors that are likely to impact future product mix in these classes. Appendix B is a new addition to the *Drug Trend Report*. This appendix provides an overview of the Medicaid program and an analysis of the prescription drug trend for Medicaid recipients from 1996 through 2001, the latest year for which data were available at the time this Report was written.

Methods

The analyses contained in the 2002 *Drug Trend Report* are based on prescription medications for a sample of Express Scripts commercial clients that maintain individual member eligibility data and use Express Scripts for both retail and mail pharmacy services. Medicaid recipients and Medicare beneficiaries receiving drug coverage through Medicare Plus Choice plans are excluded from this study because of their unique demographics and drug coverage policies. About two-thirds of the resulting 2002 sample consists of non-managed care commercial members, and about one-third is managed care commercial members.

Cost data included in past Reports were expressed on an Average Wholesale Price (AWP) ingredient cost (retail "list" price of the medication) basis. Thus, retail network discounts, mail discounts, dispensing fees, rebates and member financial contributions were not reflected in these data. This approach was adopted to ensure comparability across time periods and across client groups; however, it does not take into account that retail and mail discounts on generic products are on average about three times greater than on single-source branded products. This differential did not have a material impact on the trend percentage in past Reports because the generic fill rate was relatively stable during that period. Beginning in 2001 and extending over the next several years, however, the number of single-source brand medicines losing patent protection is growing substantially. Correspondingly, generic fill rates are increasing, reaching 45.9 percent in the fourth quarter of 2002. To take this phenomenon into account, ingredient costs were computed using a standard discount of 12 percent for brand products and 36 percent for generic products off of the AWP cost per unit, rather than computing ingredient costs on an AWP basis. Ingredient costs going back to 1998 were also re-stated using the same discount percentages to maintain comparability in the trend figures over time. When comparing these two ingredient cost calculation methodologies, the annual percentage trend figures do not vary more than 0.2 percent between 1998 and 2001. However, the brand/generic and therapeutic mix components are somewhat different because of this change in methodology. The 12 percent and 36 percent discount figures used are not meant to represent actual client discounts. Rather, they were selected primarily to reflect the roughly three to one ratio between the magnitude of brand and generic discounts that apply to the Express Scripts' book of business. Also, it should be noted that generic discount rates can vary significantly across specific products.

As was the case in previous Reports, prescriptions counts have been converted to equivalent numbers that would have been dispensed through retail pharmacies to adjust for differential mail usage rates and varying benefit structures across Express Scripts clients. Drugs sold over-the-counter and prescriptions dispensed in inpatient settings are not included in this analysis. Finally, overall figures may not represent actual client experience due to differences in plan design.

The 2002 sample consists of 3 million unique members. To prevent significant distortion in the sample, membership from any given client was limited to no more than 5 percent of the overall sample. The average age of the 2002 sample was 35, compared to the average age of 34.3 for the 2001 sample.

Trends in Expenditures for Prescription Drugs

After growing by 16.7 percent in 2001, PMPY ingredient costs rose 18.5 percent to $585.60 in 2002. As was the case in 2001, PMPY cost increases were higher for managed care clients (20.3 percent) than for other clients (17.1 percent). In 2001, however, mix and number of units per prescription accounted for the difference. The 2002 disparity was caused by the 9.2 percent utilization increase among managed care clients versus 4.7 percent for other clients. The actual net claim cost trend for Express Scripts clients ranged from a 20 percent decrease to a 35 percent increase, depending on how aggressively plan sponsors chose to implement Express Scripts' recommended cost-management programs.

The 2001-2002 PMPY ingredient cost trend was analyzed in terms of the following three dimensions:

1. Changes in the utilization of "common drugs" (medications that were available for use in 2001 and 2002)

2. Increases in ingredient costs per prescription of these common drugs

3. Introduction of "new products" to the market (drugs available for use in 2002 but not in 2001)

Utilization of common drugs was divided into two components: prevalence and intensity. Prevalence tracks the proportion of members who use one or more prescription drugs from one year to the next. Intensity is the number of prescriptions per person from one year to the next. Per prescription costs were decomposed into the relative effects of inflation, units per prescription, brand/generic mix and therapeutic mix. The impact of new drugs was divided into the independent contributions of change in per prescription cost (the differential between the cost of new drugs and the average cost of common drugs) and the added costs associated with increased utilization of new drugs (see Table 1).

Table 1
Components of Per Member Per Year Cost Trend 1997-2002*

	1997 v 1998	1998 v 1999	1999 v 2000	2000 v 2001	2001 v 2002
Inflation	5.1%	5.4%	5.4%	5.6%	7.5%
x Units per Rx	0.6%	0.2%	1.0%	0.0%	-0.1%
x Brand/Generic Mix				-1.4%	-2.3%
x Therapeutic Mix	5.0%	3.1%	5.1%	4.4%	5.3%
x Utilization	3.8%	6.2%	3.7%	6.3%	6.3%
= Common Drug	15.2%	15.6%	15.9%	15.6%	17.5%
+ New Drugs	1.6%	1.8%	0.3%	1.0%	1.0%
= All Drug	**16.8%**	**17.4%**	**16.2%**	**16.7%**	**18.5%**

* The percentage contribution of each factor does not total to the All Drug percentage increase. The calculation takes the base cost for a given year and multiplies it by one times the percentage contributed by the first factor (inflation). The resulting total is then multiplied by the percentage contributed by the second factor (number of units dispensed), and so on for each Common Drug factor. The percentage contribution of the New Drugs is then added to the total Common Drug percentage to yield an All Drug percentage increase. The final results may differ due to rounding.

The following sections discuss the degree to which each of these cost-trend components influenced cost increases for the combined non-managed and managed commercial memberships between 2001 and 2002.

Changes in Common Drug Costs Between 2001 and 2002

Utilization of Common Drugs

To ascertain the variable use patterns across therapeutic drug groupings, common drugs were categorized into therapy classes — groups of pharmaceutical agents that are chemically or therapeutically related. Products were grouped according to the first two digits of the 14-digit Generic Product Identifier (GPI) code as classified by Facts and Comparisons. This classification system defines broad drug groups used to treat similar medical conditions.

The change in overall utilization of common drugs was analyzed in terms of the relative contributions from intensity of use and prevalence of use to overall utilization. Intensity of use is calculated as the number of prescriptions divided by the number of utilizer member months, both in the aggregate and by therapy class. Prevalence is also measured on an aggregate level as well as on a therapy class basis. The change in aggregate prevalence is measured by the increase or decrease in the percentage of members who use any prescription drug in any therapy class. Change in prevalence at the therapeutic class level is measured by the change in the proportion of members who use a drug in a given therapy class. A change in the prevalence rate in a given therapy class does not necessarily translate into a change in the aggregate (all drug) prevalence rate. Members who used drugs in the specific therapy class in 2002 could have counted as a drug utilizer in 2001 due to their use of drugs in other therapy classes in 2001. For both of these measures, prevalence is calculated as the ratio of the total number of member months for all utilizers divided by the total number of member months for all members in the sample.

Common drug utilization grew by 6.3 percent from 10.59 PMPY in 2001 to 11.26 in 2002, accounting for almost one-third of the overall PMPY 2001-2002 cost growth. The level of growth, the same seen between 2000 and 2001, is similar to the level experienced in the 1998-1999 period. A slightly higher proportion of the aggregate utilization trend is attributable to increased intensity, 3.3 percent compared to prevalence which rose by 3 percent. The prevalence rate grew from 62.9 prescriptions per 100 members in 2001 to 64.8 per 100 members in 2002. Intensity increased from 1.4 prescriptions per utilizer to 1.5 per utilizer.

Wide variations were seen in the magnitude and direction of changes in utilization of common drugs between 2001 and 2002, as is true every year (see Table 2). Utilization of common drugs grew in 20 of the top 25 therapy classes in 2002. Moreover, increased utilization in the top six classes in terms of utilization — antihypertensives, antidepressants, antihyperlipidemics, gastrointestinals, narcotic analgesics and antidiabetics — accounted for almost three-fourths of the total increase in common drug utilization.

Changes in the use of cardiac-related drug classes varied significantly in 2002. The antihypertensive therapy class consists mainly of angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), vasodilators and combination products. This class continued to be the most widely prescribed therapy class at 0.86 prescriptions PMPY in 2002. The 10.6 percent increase in the use of these products reflects a steady annual increase in utilization seen over the last several years. The aging of the population and aggressive treatment of hypertension likely stimulated this strong growth pattern. As a consequence, the prevalence rate for these drugs grew by 9.7 percent to 8.7 per 100 members, while intensity remained basically flat at 0.82 prescriptions per utilizer. ACEIs continue to be the most widely used antihypertensive products because of the perception that they have superior efficacy and better side effect profiles. Although they went generic in July 2002, the combined market share of Zestril®/Prinivil® and their generic changed little after July.

The use of beta blockers and diuretics, the recommended first-line agents for uncomplicated hypertension, grew by 9.2 percent and 3.3 percent, respectively. The combined increased use of antihypertensives, beta blockers and diuretics accounted for almost one-quarter of the overall growth in common drug utilization. In contrast, the use of calcium blockers continued to decline, dropping by 1.5 percent as prevalence decreased by 1.9 percent. A recent study suggested that diuretics were more effective than ACEIs and calcium blockers as first-line treatment of hypertension.[20] Subsequent research reported that patients using ACEIs were less likely to die of heart disease than those taking diuretics.[21] Both studies may hasten the decline in the use of calcium blockers in hypertension.

Utilization of antihyperlipidemics, the third most widely used class, once again increased substantially in 2002, rising by 13 percent to 0.65 prescriptions PMPY. About 85 percent of the increase is attributable to the growing number of people who take these medications; prevalence rates for this class grew by 11 percent to 7.3 per 100 members. The dramatic increases in the use of antihyperlipidemics have been spurred by evidence that their use reduces mortality, by new guidelines that increase the total number of patients eligible for treatment and by extensive Direct-to-Consumer (DTC) advertising ($209 million from November 2001 through October 2002).[22] The market share for Lipitor® grew from 54.7 percent to 55.4 percent, while Zocor® and Pravachol® maintained their market shares at about 15.6 percent and 12.5 percent, respectively.

20 Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Journal of Clinical Hypertension* (Greenwich). 2002;4(6):393-405.

21 Nelson MR, Reid CM, Krum H, Ryan P, Wing LM, McNeil JJ. Short-term predictors of maintenance of normotension after withdrawal of antihypertensive drugs in the second Australian National Blood Pressure Study (ANBP2). *American Journal of Hypertension.* 2003;16(1):39-45.

22 CMR. as cited in: JP Morgan Securities, Inc. *Prescription Pad.* January 16, 2003.

Table 2
Utilization of Common Drugs for the Top 25 Therapy Classes 2001-2002

Ranked by 2002 PMPY Prescriptions

RANK	THERAPY CLASS	2001 Rxs PMPY	PREVALENCE % CHANGE	INTENSITY % CHANGE	2002 Rxs PMPY	TOTAL % CHANGE
1.	Antihypertensives	0.77	9.7%	0.8%	0.86	10.6%
2.	Antidepressants	0.62	10.7%	4.4%	0.72	15.6%
3.	Antihyperlipidemics	0.57	11.0%	1.8%	0.65	13.0%
4.	Gastrointestinals	0.44	9.5%	5.3%	0.50	15.3%
5.	Narcotic Analgesics	0.42	6.3%	3.1%	0.46	9.6%
6.	Antidiabetics	0.40	8.2%	0.9%	0.44	9.2%
7.	Estrogens	0.50	-4.9%	-7.0%	0.44	-11.5%
8.	Beta Blockers	0.39	8.1%	1.1%	0.43	9.2%
9.	Oral Contraceptives	0.34	11.6%	4.3%	0.40	16.3%
10.	Anti-Rheum (NSAIDs)	0.39	-4.6%	4.4%	0.38	-0.4%
11.	Diuretics	0.36	2.5%	0.8%	0.38	3.3%
12.	Antiasthmatics	0.36	3.5%	-0.8%	0.37	2.6%
13.	Thyroid	0.33	4.6%	1.0%	0.35	5.6%
14.	Antihistamines	0.33	-7.7%	9.3%	0.33	1.0%
15.	Cough/Cold	0.31	0.1%	1.1%	0.32	1.2%
16.	Calcium Blockers	0.32	-1.8%	0.3%	0.32	-1.5%
17.	Dermatologicals	0.31	-3.5%	0.0%	0.30	-3.7%
18.	Penicillins	0.30	1.6%	-1.1%	0.30	0.5%
19.	Antianxiety Agents	0.20	3.4%	1.6%	0.21	5.0%
20.	Macrolides	0.18	1.1%	-0.8%	0.18	0.4%
21.	Anticonvulsants	0.15	14.1%	0.4%	0.17	14.6%
22.	Misc. Endocrine	0.13	17.0%	3.5%	0.16	21.1%
23.	Decongestants	0.15	-2.6%	6.6%	0.15	3.8%
24.	Ophthalmic Products	0.15	-0.1%	1.1%	0.15	0.9%
25.	Cephalosporins	0.13	-1.2%	-0.6%	0.13	-1.8%
	Top 25	8.57	4.1%	2.0%	9.10	6.2%
	Other	2.03	-2.5%	9.7%	2.17	6.9%
	Total	**10.59**	**3.0%**	**3.3%**	**11.26**	**6.3%**

PMPY utilization of antidepressants grew even faster than in 2001, rising 15.6 percent in 2002 to 0.72 prescriptions PMPY. As the second most widely used therapy class, growth in antidepressant use contributed over 15 percent to the overall common drug utilization increase. About two-thirds of the rise in antidepressant use is attributable to the increased prevalence rate, 9.5 per 100 members, making it the seventh highest class in terms of prevalence. The wide use of antidepressants is partially due to a number of new indications for antidepressant use in conditions such as social anxiety disorder, premenstrual dysphoric disorder, post traumatic stress disorder and generalized anxiety disorder. This class continues to be dominated by selective serotonin reuptake inhibitors (SSRIs) such as Prozac®, fluoxetine (the generic version of Prozac®), Zoloft®, Paxil® and Celexa®, and by selective norepinephrine reuptake inhibitors (SNRIs) such as Effexor®.

The PMPY use of gastrointestinal (GI) drugs grew by 15.3 percent in 2002. The increased number of users of these drugs, 8.2 per 100 members, contributed about two-thirds to the overall use that rose to 0.5 prescriptions PMPY in 2002. DTC advertising for this class was $256 million for the 12 months ending October 2002.[23] The market share of proton pump inhibitors (Prevacid®, Prilosec®, Nexium®, Protonix® and Aciphex®) increased from 69.6 percent in 2001 to 73.9 percent in 2002 at the expense of the less expensive generic H2 blockers.

23 ibid.

Narcotic analgesics was the fifth most used therapy class. PMPY use of this class rose 9.6 percent to 0.46 prescriptions PMPY in 2002. This growth in use was due to both prevalence and intensity increases. The prevalence rate for these drugs rose by 6.3 percent to 14.1 per 100 members in 2002, while intensity increased by 3.1 percent. Neither increase is surprising given the growing reliance on these medications for treatment of patients with lower back pain, more patients being treated in outpatient settings and longer survival times for higher numbers of terminally ill patients.

The PMPY utilization of common drugs in the non-steroidal anti-inflammatory (NSAID) class actually declined marginally (-0.4 percent) in 2002 to 0.38 prescriptions PMPY after growing by only 4.9 percent in 2001. The major reason for this slight decline was that some utilization of products in this class was shifted to a new product, Bextra®. Even though Bextra® did not come to market until spring 2002, it still managed to capture 4.6 percent of the NSAID market. When Bextra® is included, NSAID utilization actually increased by 4.5 percent. Cyclooxygenase 2 inhibitors (COX-2s), Celebrex®, Bextra® and Vioxx®, continued to grow their combined market share from 41.7 percent in 2000 to 47.6 percent in 2001 to 50.6 percent in 2002.

Antidiabetic drugs, the sixth most used therapy class, experienced a 9.2 percent increase in utilization to 0.44 prescriptions PMPY in 2002. Unlike in 2001, when intensity rose more than prevalence; in 2002 the prevalence rate for antidiabetic drugs grew by 8.2 percent, whereas intensity grew by 0.9 percent. The continued rise is attributable to an increasingly obese population and the emphasis on aggressive management of diabetes, as well as to the availability of newer oral products.

Substantial changes took place in the 2002 PMPY utilization of common drugs in several drug classes pertaining to women's health. The use of oral contraceptives increased by 16.3 percent to 0.4 prescriptions PMPY. This was due mostly to the 11.6 percent increase in the prevalence rate, likely reflecting more coverage of oral contraceptives by plan sponsors. Estrogen use dropped from the fourth highest used therapy class in 2001 to the seventh ranked class in 2002. This dramatic shift reflects an 11.5 percent decline in estrogen use to 0.44 prescriptions PMPY in 2002. The declining use of these products includes drops in prevalence and intensity, and corresponds to the release of two studies that called into question the use of combination estrogen/progestin hormone replacement therapy (HRT). In large part because of the fallout from these studies, many women who were using HRT products, or who would have started taking those products, instead used miscellaneous endocrines. A study conducted by Express Scripts revealed that 36 percent of women in a sample of Express Scripts members stopped using HRT combination products, more than four times the discontinuation rate during the same period the preceding year. On the other hand, 57 percent continued using the HRT combination products. The remainder switched to other products. These data suggest that when the longer-term risk of using HRT combination products was better understood, large numbers of women and their physicians acted promptly to avoid HRT and reduce their risk. Although these studies found no adverse effects among users of estrogen alone, 22.6 percent of an Express Scripts member sample discontinued use of any estrogen product and did not switch to a combination HRT product or to another agent used to treat osteoporosis. This was more than double the discontinuation rate for the same period in the previous year.

This changed behavior was manifest in the 21.1 percent increase in the use of miscellaneous endocrines — particularly the use of products used to treat and prevent osteoporosis, such as Fosamax®, Evista® and Actonel®, which had a combined 86.7 percent market share in 2002 compared to their 83.3 percent level in 2001. Other types of drugs in this class are growth hormones and fertility agents. This follows the 30.1 percent increase in miscellaneous endocrines in 2001, when much conjecture was circulating about possible long-term HRT side effects, but no strong scientific proof had yet been released. Thyroid use continued to grow in 2002, reaching 0.35 prescriptions PMPY. Most of this rise was due to the 4.6 percent increase in prevalence to 3.6 per 100 members.

Antiasthmatic drugs, the twelfth most used class, experienced a modest 2.6 percent increase in use to 0.37 prescriptions PMPY in 2002. This entire rise was attributable to increased numbers of utilizers, reflecting the central role that prescription drug therapy plays in asthma control. The use of controllers such as Singulair® and Advair Diskus® grew considerably, by 16.5 percent and 12.6 percent, respectively.

The use of common antihistamine products, consisting overwhelmingly of low- and non-sedating brand products, remained flat at 0.33 prescriptions PMPY in 2002. However, the utilization figure does not take into account the market entry of Clarinex® in 2002. When Clarinex® is included, PMPY utilization of antihistamines actually rose by 11.3 percent. In the 12 months ending in October 2002, $329 million was spent on DTC advertising for this class.[24] In December 2002, Claritin® was marketed as an over-the-counter (OTC) product.

After declining in 2000 and 2001, the PMPY use of products in the cough/cold class rose by a marginal 1.2 percent in 2002. Yet, with a 0.32 prescriptions PMPY utilization rate, cough/cold products still ranked as the fifteenth most used category of drugs, with 13.8 per 100 members taking drugs in this class. Generics continue to dominate the class, increasing their collective market share from 51.6 percent in 2001 to 53.5 percent in 2002 at the expense of Claritin-D®, Allegra-D® and Zyrtec-D®. Utilization of decongestants, a class consisting primarily of nasal steroids used to alleviate allergy symptoms, increased by 3.8 percent to 0.15 prescriptions PMPY in 2002. Unlike 2001, the 2002 rise was due solely to the increased intensity of use, as the number of people using these products declined 2.6 percent. Flonase® and Nasonex® continued to dominate this class with a combined market share of 60.3 percent.

24 ibid.

The PMPY use of anticonvulsants grew by another 14.6 percent to 0.17 prescriptions PMPY in 2002 after increasing by 10.7 in 2001. Virtually all of this rise was due to growing numbers of utilizers of these products. This rise was fueled by wider use of Neurontin® as a pain control medication. The market share for Neurontin® grew from 22.5 percent in 2000 to 25.4 percent in 2001 to 26.3 percent in 2002. The market share for Topamax® rose from 4.6 percent to 7 percent. This drug is indicated for the treatment of epilepsy, but it is often used for migraine pain and it may be used for weight control.

PMPY utilization of the use of drugs in the macrolide antibiotic class was flat in 2002. Only a marginal 0.5 percent growth was evident in PMPY penicillin utilization, and a 1.8 percent decline was seen in the use of cephalosporins.

Ingredient Cost Per Prescription

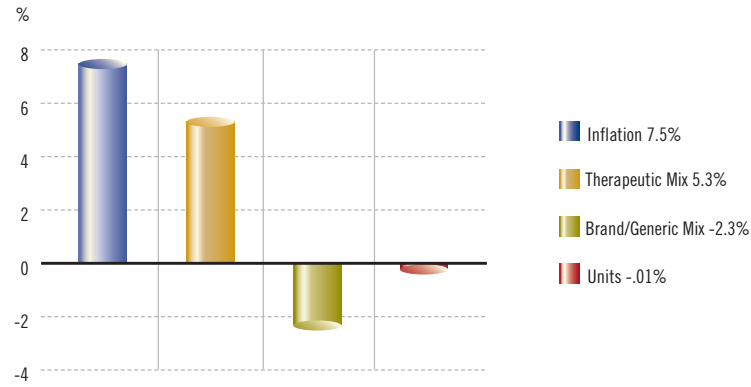
Between 2001 and 2002, 60.5 percent of the overall PMPY ingredient cost rise was due to growth in per prescription costs, virtually the same as was the case between 2000 and 2001.

Components of the trend in the cost per prescription for common drugs are:

- **Inflation** (changes in the unit price charged for brands and generics available in both 2001 and 2002)
- **Brand/Generic Mix** (changes in the mix of brands and generics due to greater market share penetration of existing generics or the introduction of new generics)
- **Therapeutic Mix** (changes in the mix of chemical entities within and across therapeutic classes, and the introduction of new dosage forms for existing chemical entities)
- **Units** (the number of units dispensed per prescription)

Inflation had by far the greatest impact on the average ingredient cost per prescription for common drugs between 2001 and 2002, followed by therapeutic mix, brand/generic mix and the number of units per prescription (see Figure 6 and Table 3). The relative contributions of these factors to the overall increase in the average prescription ingredient cost for common drugs, and their variable impacts across therapy classes, are described on the following pages.

Figure 6
Percent Change in Ingredient Cost Per Prescription Due to Inflation, Therapeutic Mix, Brand/Generic Mix and Units 2001-2002



Inflation

The calculation of inflation in this Report is based on Average Wholesale Price (AWP) that First DataBank reports for each unit of a given product. This AWP per unit for each drug was then discounted 12 percent for brand drugs and 36 percent for generics. The inflation rate in this Report represents the difference between the weighted average discounted AWP per unit in 2001 and the weighted average discounted AWP price per unit in 2002 for common drugs, holding constant market share and units per prescription. The resulting inflation rate was 7.5 percent in 2002, marking the fifth consecutive year that inflation topped 5 percent. Based on Consumer Price Index (CPI) statistics reported by the U.S. Department of Labor (which defines inflation somewhat differently than this analysis), the inflation rate for prescription drugs was 5.2 percent in 2002. This level contrasts with the 4.6 percent inflation rate experienced in overall medical care.[25]

Inflation contributed 71.8 percent to the overall increase in the cost per prescription in 2002. As has been true in the past, inflation rates vary widely across brands and generics as well as by therapy class. In 2002, inflation was 8.4 percent for brand drugs and 3.1 percent for generics. As shown in Table 3 and Table 4, price increases were evident in all of the top 25 therapy classes. These increases ranged from 3.6 percent for calcium blockers to 13.5 percent for cough/cold and cephalosporins.

25 Bureau of Labor Statistics. U.S. Department of Labor. Consumer price index-all urban consumers (current series). Available at: http://www.bls.gov/cpi/home.htm#overview. Accessed February 20, 2003.

Table 3
Price Changes Due to Inflation for the Top 25 Therapy Classes 2001-2002

Ranked by Percent Change

RANK	THERAPY CLASS	PRICE % CHANGE BRAND PRODUCTS	PRICE % CHANGE GENERIC PRODUCTS	PRICE % CHANGE ALL PRODUCTS
1.	Cough/Cold	14.8%	7.7%	13.5%
2.	Cephalosporins	17.2%	5.6%	13.5%
3.	Estrogens	12.7%	3.6%	12.2%
4.	Antihistamines	11.5%	61.6%	11.8%
5.	Decongestants	11.0%	-60.9%	11.0%
6.	Ophthalmic Products	10.6%	3.4%	9.8%
7.	Thyroid	6.7%	18.8%	9.2%
8.	Anticonvulsants	9.8%	2.0%	8.9%
9.	Dermatologicals	10.5%	-2.2%	8.8%
10.	Gastrointestinals	9.6%	0.5%	8.7%
11.	Antihypertensives	9.1%	0.9%	7.6%
12.	Antiasthmatics	8.6%	2.1%	7.6%
13.	Antidepressants	7.4%	3.6%	7.0%
14.	Oral Contraceptives	7.5%	3.7%	6.9%
15.	Antianxiety Agents	6.7%	6.5%	6.6%
16.	Antidiabetics	6.7%	0.5%	6.2%
17.	Anti-Rheum (NSAIDs)	7.3%	1.2%	6.2%
18.	Antihyperlipidemics	6.3%	2.6%	6.2%
19.	Beta Blockers	6.3%	4.9%	5.5%
20.	Penicillins	5.5%	4.1%	5.3%
21.	Narcotic Analgesics	6.7%	1.5%	5.0%
22.	Diuretics	13.9%	2.0%	4.8%
23.	Misc. Endocrine	4.7%	0.3%	4.7%
24.	Macrolides	4.2%	-0.5%	4.2%
25.	Calcium Blockers	3.7%	3.4%	3.6%
	Top 25	8.5%	3.0%	7.5%
	Other	8.1%	3.1%	7.6%
	Total	**8.4%**	**3.1%**	**7.5%**

In general, therapy classes consisting of drugs used to treat respiratory conditions (cough/cold products, antihistamines, decongestants and antiasthmatics) experienced the greatest inflation increases in 2002. Cough/cold products and antihistamines, both dominated by low- and non-sedating antihistamine products, had inflation increases greater than 11 percent. As shown in Table 4, the most commonly dispensed versions of Claritin® and Claritin-D® 24 Hour both had 21.1 percent increases in 2002. These increases came after the introduction of the lower price product Clarinex® in early 2002 and before the introduction of OTC versions and the withdrawal of prescription versions for both Claritin® and Claritin-D® 24 Hour in late 2002. The generic inflation within the antihistamine class was due to dramatic cost increases for the generic promethazine. Price increases by the generic manufacturers of this product averaged almost 180 percent. However, the relatively small market share of this product, less than 5 percent, resulted in little impact on the class as a whole.

Table 4

Price Changes for the Top 50 Common Brand Drugs 2001-2002

Ranked by Number of Prescriptions

	Product	Unit Price On 12/31/2001	Unit Price On 12/31/2002	Percent Change	# of Price Changes Between 12/31/2001 and 12/31/2002
1.	LIPITOR® 10MG	2.03	2.31	13.5%	2
2.	LIPITOR® 20MG	3.14	3.44	9.4%	2
3.	PREVACID® 30MG	4.14	4.63	11.7%	2
4.	ORTHO TRI-CYCLEN®	1.16	1.32	13.5%	2
5.	ZITHROMAX® 250MG	6.97	7.33	5.0%	2
6.	PRILOSEC® 20MG	4.30	4.61	7.3%	1
7.	CELEBREX® 200MG	2.75	2.88	4.6%	1
8.	ZYRTEC® 10MG	1.98	2.04	3.0%	2
9.	PREMARIN® 0.625MG	0.76	0.89	17.5%	2
10.	CLARITIN® 10MG	2.67	3.23	21.1%	3
11.	FOSAMAX® 70MG	16.19	17.14	5.9%	1
12.	VIOXX® 25MG	2.75	2.88	4.5%	1
13.	ALLEGRA® 180MG	2.19	2.35	7.3%	2
14.	PREMPRO® 0.625-2.5 MG	1.18	1.30	10.0%	2
15.	ALBUTEROL® 90MCG	1.26	1.26	0.0%	0
16.	NORVASC® 5MG	1.41	1.45	3.0%	2
17.	NEXIUM® 40MG	4.00	4.42	10.6%	2
18.	FLONASE® 50MCG	3.61	4.06	12.7%	2
19.	ZOLOFT® 100MG	2.49	2.52	1.4%	2
20.	CELEXA® 20MG	2.25	2.41	7.3%	2
21.	TOPROL XL® 50MG	0.65	0.74	12.9%	3
22.	PAXIL® 20MG	2.72	2.82	4.0%	1
23.	WELLBUTRIN SR ®150MG	1.68	1.92	13.8%	2
24.	ZOLOFT® 50MG	2.42	2.52	4.3%	2
25.	NORVASC® 10MG	2.17	2.17	0.0%	1
26.	LIPITOR® 40MG	3.50	3.64	4.2%	2
27.	GLUCOPHAGE XR® 500MG	0.69	0.77	11.0%	1
28.	PRAVACHOL® 40MG	4.14	4.35	5.0%	1
29.	PROTONIX® 40MG	3.13	3.51	12.2%	3
30.	SYNTHROID® 100MCG	0.39	0.42	6.7%	2
31.	NASONEX® 50MCG	3.52	4.04	14.8%	4
32.	PRAVACHOL® 20MG	2.55	2.89	13.4%	2
33.	LEVAQUIN® 500MG	8.88	10.08	13.5%	2
34.	CLARINEX® 5MG	2.19	2.28	4.2%	1
35.	TOPROL XL® 100MG	0.98	1.11	12.9%	3
36.	ALLEGRA-D® 120-60MG	1.23	1.38	12.5%	2
37.	CELEXA® 40MG	2.34	2.52	7.3%	2
38.	CIPRO® 500MG	4.67	5.47	17.0%	2
39.	DIFLUCAN® 150MG	12.28	13.14	7.0%	2
40.	FLOMAX® 0.4MG	1.77	1.90	7.1%	2
41.	EFFEXOR XR® 75MG	2.62	2.85	9.0%	2
42.	ZESTRIL® 10MG	1.01	1.15	13.5%	2
43.	ALLEGRA® 60MG	1.18	1.36	14.6%	2
44.	CLARITIN-D 24 HOUR® 240-10MG	3.00	3.64	21.1%	3
45.	AUGMENTIN® 875-125MG	5.40	5.61	4.0%	1
46.	ACCUPRIL® 20MG	1.05	1.15	9.4%	2
47.	TRICOR® 160MG	2.49	2.74	10.1%	3
48.	SINGULAIR® 10MG	2.75	2.91	5.9%	1
49.	PREMARIN® 1.25MG	1.05	1.23	17.5%	2
50.	SYNTHROID® 75MCG	0.38	0.41	6.7%	2

Decongestants also experienced double-digit inflation in 2002. The prices for the top two products in this class, Flonase® and Nasonex®, rose 12.7 percent and 14.8 percent, respectively. These two products accounted for over 60 percent of the utilization in this class and contributed significantly to the inflation trend. However, it must be noted that prices for all of the products that accounted for over 99 percent of the prescriptions in the class increased by more than 10 percent in 2002.

Antiasthmatics were led by price increases in Combivent® and Atrovent®, branded products containing the active ingredient ipratropium. Prices for both products increased by 21.9 percent in 2002. Prices for the market share leaders in the class, Singulair® and Advair Diskus®, rose 5.9 percent and 9.4 percent, respectively.

The class with the highest brand inflation rate was cephalosporins, which are used to treat bacterial infections. The price for the leading brand in the class, Cefzil®, grew 13.4 percent in 2002. The price for Ceftin®, which went generic in 2002, increased by 7.1 percent.

Inflationary increases for other anti-infective classes, penicillins and macrolides, were much lower than for cephalosporins. The brand market share for penicillins continued to be dominated by Augmentin®, the price of one strength of which rose by 4 percent. Some strengths of Augmentin® came out in generic form in 2002. Among macrolides, the price of the most frequently dispensed version of Zithromax® increased 5 percent, and the price of Biaxin® XL, the newest formulation in the Biaxin® family, rose by 4.1 percent in 2002.

Estrogens and thyroid products continued to rank in the top 10 in 2002. Estrogens, while remaining in the same rank position as last year, increased 2.8 percentage points more than last year. Increases for the most commonly dispensed strengths of the estrogen market leader, Premarin®, ranged from 17.5 percent to 23.9 percent. The price increase for the combination estrogen-progestin product Prempro® 0.625-2.5 MG, the second most used product in the class, was 10 percent. Thyroid products experienced the largest decline in the rate of price increase for any of the top 25 therapeutic classes. The 9.2 percent price increase was 10.2 percentage points lower than in 2001. This was primarily due to the relatively small 6.7 percent increase seen for Synthroid® 100MCG. Synthroid® is the dominant product in the class with over 60 percent of market share. In contrast, the inflation rate for generic thyroid products rose 18.8 percent. This increase was led by the branded generic, Levoxyl®, with a 20.1 percent increase. Two other classes of drugs devoted to caring for women's health — contraceptives and miscellaneous endocrines — experienced relatively low inflationary increases of 6.9 percent and 4.7 percent, respectively.

Ophthalmic products ranked sixth in the magnitude of price increases, in large part due to a 10.6 percent rise in prices of brand ophthalmic products. Brand ophthalmics can be grouped into three basic categories: products used to treat glaucoma (eye pressure), products used to treat itchiness associated with allergies and products used to treat infections. Of these categories, products used to treat infections increased in price the most. Ciloxan® and Ocuflox®, both quinolone antibiotics, increased 18.2 percent and 14.5 percent, respectively. The price of Tobradex®, a different type of antibiotic, increased 18.4 percent. By comparison, the price rises were 5.9 percent for Xalatan®, the most frequently dispensed glaucoma product, and 9.2 percent for the most frequently dispensed allergy symptom reliever, Patanol®.

Increases in brand prices were also seen among anticonvulsants, with brand inflation rising 9.8 percent. Prices for the most widely dispensed strengths of Neurontin®, the brand commanding 26.3 percent of the market share in the class, grew by 10.5 percent in 2002. Topamax®, the product with the biggest market share growth in the class at 7 percent, increased in price by 16.3 percent in 2002.

Dermatological brand price increases reached double figures in 2002, increasing by 10.5 percent. Bactroban®, the most frequently dispensed brand in the class, increased only 6 percent. However, this modest price rise was offset by increases of 13.1 percent for the acne medication, Differin® and 44.2 percent for the topical antiviral, Zovirax®.

Gastrointestinal drugs increased in price by 8.7 percent, with brand prices growing 9.6 percent. Of the top four proton pump inhibitors, only the Prilosec® price increase, 7.3 percent, was less than 10 percent.

None of the drug classes used to treat cardiac conditions fell into the top 10 highest in terms of inflation. The only outlier was branded diuretics. This was due to the 9.4 percent increase in the price of Demadex®, which went generic in 2002. However, due to heavy generic use in this class, the Demadex® price increase did not have a significant impact on the class as a whole.

Classes used to treat conditions affecting the central nervous system (CNS) also did not appear in the top 10 highest in terms of inflation. These classes include antidepressants at 7 percent and antianxiety agents at 6.6 percent. Of note, however, was the 6.5 percent increase in the cost of generic antianxiety agents. This increase was driven by an average increase of almost 250 percent in the product hydroxyzine, an antihistamine used to treat hives, motion sickness and insomnia, as well as anxiety. This extraordinary price hike occurred as several generic manufacturers dropped out of the market, leaving only one producer.

Similarly, no classes with primary indications in pain relief, including anti-rheumatics (NSAIDs) and narcotic analgesics, had unusually high inflation increases. Among NSAID brands, a 19.8 percent increase occurred in the price for the most commonly used strength of Mobic®, a relatively new drug on the market. However, because of the modest 3 percent market share held by Mobic®, its impact on the overall class inflation rate was minor. Among COX-2s, the most commonly dispensed drugs in the class, competitive pressures kept all products below a 7 percent increase.

Within the narcotic analgesics class, the price for Ultram® rose by 24.9 percent, even though Ultram® went generic in mid-2002. The price for its sister product, Ultracet®, increased by 14.6 percent. In this class, with a generic fill rate approaching 70 percent, generic prices increased on average by only 1.5 percent.

Drug Mix

The impact of mix on changes in the cost per prescription was analyzed in terms of therapeutic mix and brand/generic mix. Therapeutic mix is the use of relatively more expensive or less expensive drugs, and drug strengths within and across therapy classes. Brand/generic mix refers to cost changes caused by shifts from brands to their respective generic equivalents both within and across therapy classes.

Therapeutic Mix

The 5.3 percent therapeutic mix trend in 2002 was a little higher than the 4.4 percent seen in 2001. As has been the case in past years, significant variability in therapeutic mix existed across therapy classes in 2002. On one extreme, the therapeutic mix trend was negative in nine classes, and on the other it was over 5 percent in four classes.

Table 5
Price Changes Due to Therapeutic Mix for the Top 25 Therapy Classes 2001-2002

RANK	THERAPY CLASS	THERAPEUTIC MIX % CHANGE
1.	Antiasthmatics	12.3%
2.	Anticonvulsants	8.7%
3.	Narcotic Analgesics	7.1%
4.	Antidiabetics	6.1%
5.	Ophthalmic Products	4.5%
6.	Antihyperlipidemics	4.2%
7.	Antihypertensives	3.4%
8.	Antidepressants	2.6%
9.	Penicillins	2.4%
10.	Beta Blockers	2.2%
11.	Gastrointestinals	1.7%
12.	Calcium Blockers	1.2%
13.	Decongestants	1.0%
14.	Anti-Rheum (NSAIDs)	0.6%
15.	Misc. Endocrine	0.5%
16.	Oral Contraceptives	0.4%
17.	Thyroid	-0.4%
18.	Antianxiety Agents	-0.7%
19.	Diuretics	-0.8%
20.	Macrolides	-0.9%
21.	Cephalosporins	-1.7%
22.	Antihistamines	-2.5%
23.	Dermatologicals	-2.6%
24.	Cough/Cold	-2.9%
25.	Estrogens	-4.7%
	Top 25	4.0%
	Other	9.4%
	Total	**5.2%**

The drug which contributed the most to the 12.3 percent mix increase in antiasthmatics was Advair Diskus®, a relatively new combination product containing the active ingredients of two other asthma drugs, Flovent® and Serevent®. While Advair Diskus® was one of the most expensive products in the class at $124.09 per inhaler, this price was less than the combined price of Flovent® and Serevent®. Also, the switch to Advair Diskus® was the primary reason for the decline in intensity, or prescriptions per person, in this class due to patients requiring only one prescription rather than two. Another contributor to the mix increase in this class, although not to the extent of Advair Diskus®, was Singulair®. Like Advair Diskus®, Singulair® is indicated for the prevention of asthma attacks, not for acute therapy. In addition, Singulair®, which received an indication for allergic rhinitis in 2003, likely was used more frequently for such off-label conditions in 2002.

The second highest ranked class in terms of therapeutic mix was anticonvulsants, which saw an 8.7 percent increase in 2002. While no one product increased market share to the extent seen within the antiasthmatic class, all six of the anticonvulsant drugs that had average costs of more than $100 per prescription in 2002, gained market share. These drugs are characterized by their use in treating a broad range of conditions other than seizures. The most frequently prescribed anticonvulsant, Neurontin®, often used to treat pain, saw its market share rise 0.9 percent. Topamax®, used to prevent migraines, gained 2.4 market share points. At $162.22 per prescription, the cost for Topamax® was almost twice the therapy class average price of $82.73.

Narcotic analgesics were the third highest class in terms of mix trend at 7.1 percent. This high mix trend was due primarily to Duragesic®, which rose in market share by only 0.2 percent but which carries a price that is over seven times the class average. Also contributing to the mix increase was a 0.9 percent increase in the market share of tramadol products, which include Ultram®, tramadol-generic and Ultracet®.

The last class with mix trend greater than 5 percent was antidiabetics. Market share increases were seen among the most expensive oral products and the most expensive insulin products. Among oral antidiabetics, Actos® and Avandia® increased market share by 1.3 percent and 0.2 percent, respectively. The average per prescription cost for Actos® was 2.3 times the average cost in the class, while the cost of Avandia® was 1.9 times greater than the class average. Among insulins, Humalog® and Novolog® continued to take market share from Humulin® and Novolin®. These newer products cost about twice as much as their predecessors but deliver insulin much faster, thereby simplifying many of the timing issues associated with injecting insulin at meal times.

Classes with the greatest negative mix trend were ones in which the previous market leader fell out of favor due to negative publicity or loss of marketing support. In the case of estrogens, which experienced a 4.7 percent drop in mix trend, adverse publicity about the side effects of combination estrogen/progestin products contributed to market share declines of 3.7 percent and 0.2 percent for Prempro® and Premphase®, respectively. Likewise, in the dermatological class, concerns about the safety of Accutane® (and all isotretinoin products) precipitated a 0.5 percent drop in isotretinoin market share. This relatively small decrease was magnified by the cost of Accutane®, which at $414.14 per prescription was 8.4 times the class average.

Antihistamines and cough/cold products had similar mix trend decreases in 2002 due to precipitous declines in the Claritin® franchise. In both classes, Claritin® products were the most frequently dispensed as well as the most expensive products in their respective classes in 2001. In 2002, however, Claritin® dropped 8.4 points largely to the new drug Clarinex®, made by the same manufacturer. As a byproduct, market shares for the remaining non- and low-sedating common drug products Allegra® and Zyrtec® rose by 5.5 percent and 1.9 percent, respectively. In the cough/cold class, Claritin-D® 24 Hour and Claritin-D® 12 Hour dropped a combined 4 percent. Since no follow-on product was produced by the manufacturer of Claritin-D®, this lost market share was captured by Allegra-D® and Zyrtec-D®.

Brand/Generic Mix

The overall brand/generic mix was -2.3 percent, as 22 of the top 25 therapy classes experienced a decline in brand/generic mix trend. In general, the financial impact of a new generic on annual drug trend depends on the price of the brand relative to the generic equivalent, the speed of converting the predecessor brand to its generic equivalent (generic conversion rate), the date the generic was introduced and the original market share of the brand. The remainder of this section outlines the effect that the introductions of significant new generics have had in reducing prescription drug costs.

Table 6
Brand/Generic Mix for the Top 25 Therapy Classes 2001-2002

RANK	THERAPY CLASS	% CHANGE
1.	Antianxiety Agents	-9.1%
2.	Antidiabetics	-7.6%
3.	Penicillins	-6.0%
4.	Narcotic Analgesics	-5.6%
5.	Oral Contraceptives	-5.5%
6.	Antidepressants	-5.1%
7.	Cephalosporins	-5.0%
8.	Antihypertensives	-4.6%
9.	Diuretics	-2.8%
10.	Anti-Rheum (NSAIDs)	-2.0%
11.	Calcium Blockers	-2.0%
12.	Cough/Cold	-1.7%
13.	Dermatologicals	-1.6%
14.	Gastrointestinals	-1.2%
15.	Thyroid	-1.1%
16.	Ophthalmic Products	-1.0%
17.	Anticonvulsants	-0.8%
18.	Antihyperlipidemics	-0.6%
19.	Antiasthmatics	-0.5%
20.	Antihistamines	-0.2%
21.	Estrogens	-0.2%
22.	Decongestants	-0.1%
23.	Macrolides	0.1%
24.	Misc. Endocrine	0.1%
25.	Beta Blockers	0.9%
	Top 25	-2.5%
	Other	-1.3%
	Total	**-2.3%**

The highest brand/generic mix was in the antianxiety class, -9.1 percent. The key factor that made antianxiety agents the leader in brand/generic mix was the substantial price difference between BuSpar® and its generic, buspirone. The 18.5 percent AWP difference between the brand and the generic was much higher than the 10 percent typically seen for new generics.

The substantial -7.6 brand/generic mix in the antidiabetic class was driven largely by the conversion of Glucophage® to metformin. About 90 percent of Glucophage® prescriptions were converted to metformin within 6 months of the generic's entry into the market in late January 2002.

The brand/generic mix of -6 percent for penicillins was due to the introduction of generics for some strengths of Augmentin®. Generics for Augmentin® did not achieve maximum impact in 2002, largely because the introduction came on the heels of an unexpected loss of a patent infringement lawsuit by the brand manufacturer. This decision resulted in supply shortages in the first few months of generic availability and, consequently, a slower generic uptake.

The introduction of tramadol, the generic for Ultram®, led to the -5.6 percent brand/generic mix in the narcotic analgesic class. Tramadol was produced by multiple manufacturers shortly after generic launch, and a 90 percent generic conversion was achieved within 5 months. The factors keeping the brand/generic mix for narcotic analgesics from being even higher were the relative low (6.9 percent in 2001) market share for Ultram® and a mid-year launch for tramadol.

The -5.5 percent brand/generic mix for oral contraceptives was achieved despite a slow uptake for generic Loestrin Fe®. Slower uptake is typically seen for contraceptives because of the wide range of products in the class and the branding of the generic (Microgestin® FE), which blurs the differentiation between the brand and generic versions.

The brand/generic mix for antidepressants was -5.1 percent. This significant brand/generic mix was largely driven by the use of fluoxetine, the generic for Prozac®.

The impact of the generic for Ceftin®, at -5 percent, was enough to capture seventh place for cephalosporins in the brand/generic mix ranking. However, two factors kept this impact from being greater. First, only Ceftin® tablets and capsules went generic in 2002 accounting for an overall slower generic uptake than if all Ceftin® dosage forms had gone generic at the same time. Second, the overall market share of generic and brand Ceftin® decreased from 13.3 percent in 2001 to 11.4 percent in 2002.

The launch of lisinopril, the generic for the co-branded products Zestril® and Prinivil®, resulted in one of the fastest conversions ever seen for a new generic. A 90 percent conversion was achieved in 4 months. Only the mid-year launch of the generic prevented the antihypertensive class from a higher ranking among the top eight classes. Yet the -4.6 percent brand/generic mix was still considerable.

As the impact of new generics on trend is analyzed for other classes, market share dynamics and release dates must be considered. For example, diuretics were already more than 80 percent generic, so the introduction of a generic for Demadex® did not have a major effect on the class, which had a -2.8 percent brand/generic mix. Among anti-rheumatics, COX-2s have largely supplanted traditional NSAIDs as the drugs of choice, thereby dampening the impact of generic Relafen® (-2 percent brand/generic mix). In the antihyperlipidemic class, Mevacor® lost market share as its manufacturer shifted marketing efforts to Zocor®. So again, the result of a new generic was not as significant, leading to only a -0.6 percent brand/generic mix.

The launch of the branded generic for Accutane®, Amnesteem™, was hampered by strict labeling requirements warning of potential safety issues with all oral isotretinoin products — both brand and generic. This disadvantage, coupled with a late 2002 release date, reduced the impact of the generic to a -1.6 percent brand/generic mix in the dermatological class.

Within the gastrointestinal class, the mid-December release date of the generic for Prilosec® lessened the effect of this release on the brand/generic mix to only -1.2 percent. The generic for Axid®, a member of the H2 category of drugs that had significant decreases in utilization in favor of PPIs, contributed to most of the trend impact because it was released in mid-2002.

At the other end of the brand/generic mix spectrum was the beta blocker class. In this class the brand/generic mix was positive, at 0.9 percent. This is indicative of market share moving back to a brand version of a drug when an established generic is already on the market. This unexpected event actually occurred due to a supply shortage in 2002 of long-acting propranolol capsules. In this case, the brand, Inderal LA®, became more readily available, so it was dispensed in a greater proportion than the generic.

Units Per Prescription

The -0.1 percent difference in the cost per prescription due to changes in the number of units per prescription was the first time that this factor was negative since the inception of the *Drug Trend Report* in 1997.

Table 7
Changes in Units Per Prescription for the Top 25 Therapy Classes 2001-2002

Ranked by Percent Change

RANK	THERAPY CLASS	% PRESCRIPTIONS	% CHANGE
1.	Narcotic Analgesics	4.1%	4.7%
2.	Cough/Cold	2.8%	3.7%
3.	Dermatologicals	2.7%	2.1%
4.	Macrolides	1.6%	1.7%
5.	Anti-Rheum (NSAIDs)	3.4%	1.1%
6.	Decongestants	1.4%	1.0%
7.	Antidiabetics	3.9%	0.7%
8.	Beta Blockers	3.8%	0.6%
9.	Antihistamines	3.0%	0.6%
10.	Estrogens	3.9%	0.5%
11.	Antianxiety Agents	1.9%	0.5%
12.	Penicillins	2.6%	0.2%
13.	Oral Contraceptives	3.6%	0.0%
14.	Calcium Blockers	2.8%	-0.1%
15.	Antihypertensives	7.6%	-0.2%
16.	Gastrointestinals	4.5%	-0.4%
17.	Antiasthmatics	3.3%	-0.4%
18.	Thyroid	3.1%	-0.4%
19.	Antihyperlipidemics	5.8%	-0.7%
20.	Anticonvulsants	1.5%	-0.8%
21.	Diuretics	3.3%	-1.1%
22.	Misc. Endocrine	1.4%	-1.5%
23.	Ophthalmic Products	1.4%	-2.0%
24.	Antidepressants	6.4%	-2.0%
25.	Cephalosporins	1.1%	-3.5%
	Top 25	81.0%	0.0%
	Other	19.0%	-0.5%
	Total	**100.0%**	**-0.1%**

Leading the negative trend in units per prescription were some classes of antibiotics. This trend may be a result of changes in dosing recommendations — particularly for drugs in the cephalosporin and macrolide classes. Several of these drugs are just as effective when used for shorter periods, but compliance is improved and the risk of resistance is reduced. For example, the macrolide Zithromax® is used for only 5 days for many infections. Some spillover into other classes of antibiotics may be occurring.

The negative trend in units per prescription for antidepressants may be explained by the recent availability of products such as Prozac® Weekly™ and Paxil CR™. These long-acting products are taken by patients who previously would have required prescriptions with a greater unit count. Patients who take shorter-acting antidepressants still require prescriptions for one or more units per day.

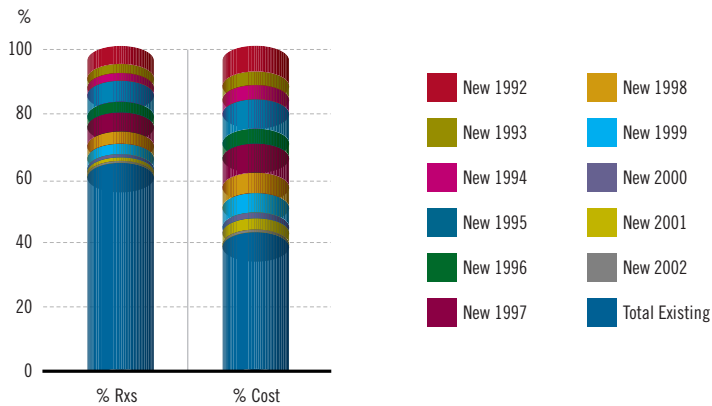
Classes with the greatest increase in units trend are narcotic analgesics, cough/cold products and dermatologicals. All three classes consist of products generally taken on an "as needed" basis, rather than for a specified period of time. These three classes consistently rank among the top five classes in units trend.

New Drugs

Drugs introduced in 1992 and thereafter accounted for 57.7 percent of 2002 PMPY costs and 36.2 percent of total 2002 PMPY utilization (see Figure 7). In contrast to the robust cumulative impact that new drugs introduced between 1992 and 2001 had on 2002 costs and utilization, the annual impact of drugs introduced in 2002 was marginal. Drugs introduced in 2002 accounted for only one percent of the overall 18.5 percent 2002 trend. Ninety percent of this contribution was due to the utilization of these new drugs, with the remaining 10 percent attributable to added costs per prescription (see Table 8). This relatively small percentage continued a downward trend that began in 1997. Following the FDA's approval of 24 new drugs[26] and eight new biologics[27] in 2001, only 17 new drugs[28] and nine new biologics[29] were approved in 2002 — the lowest number of new drug approvals since 1983.

Figure 7

Impact of New Drugs Introduced Since 1992 on 2002 Utilization and Ingredient Cost



26 Center for Drug Evaluation and Research. U.S. Food and Drug Administration. NMEs approved in calendar year 2001. Published January 2002. Available at: www.fda.gov/cder/rdmt/NMECY2001.HTM. Accessed February 27, 2002.

27 Center for Biologicals Evaluation and Research. U.S. Food and Drug Administration. 2001 Biological License Application Approvals. Last Updated January 31, 2003. Available at: http://www.fda.gov/cber/appr2001/2001lic.htm. Accessed March 25, 2003.

28 Center for Drug Evaluation and Research. U.S. Food and Drug Administration. NMEs approved in calendar year 2002. Available at: www.fda.gov/cder/rdmt/NMECY2002.HTM. Accessed February 21, 2003.

29 Center for Biologicals Evaluation and Research. U.S. Food and Drug Administration. 2002 Biological License Application Approvals. Last Updated January 31, 2003. Available at: http://www.fda.gov/cber/appr2002/2002lic.htm. Accessed March 25, 2003.

Table 8
Top New Drugs in 2002

RANK	DRUG NAME	ROUTE	FDA APPROVAL DATE	PRIMARY INDICATION	% INGREDIENT COST	PMPY COST
1.	CLARINEX®	PO	8-Feb-02	Allergic Rhinitis	0.33%	$1.93
2.	BEXTRA®	PO	16-Nov-01	Arthritis	0.26%	$1.54
3.	LEXAPRO®	PO	14-Aug-02	Depression	0.05%	$0.28
4.	ELIDEL®	TP	13-Dec-01	Atopic Dermatitis	0.04%	$0.26
5.	NEULASTA®	SQ	31-Jan-02	Leukopenia	0.03%	$0.19
6.	ORTHO EVRA®	TD	20-Nov-01	Contraception	0.02%	$0.12
7.	ADVICOR®	PO	17-Dec-01	Elevated Cholesterol	0.01%	$0.08
8.	BENICAR®	PO	25-Apr-02	Hypertension	0.01%	$0.05
9.	ZELNORM®	PO	24-Jul-02	Irritable Bowel Syndrome	0.01%	$0.05
10.	FROVA®	PO	8-Nov-01	Migraine Headache	0.01%	$0.04
11.	TRI-LUMA®	TP	18-Jan-02	Skin Discoloration	0.01%	$0.03
12.	ZETIA®	PO	25-Oct-02	Elevated Cholesterol	0.01%	$0.03
13.	SUBUTEX®	SL	8-Oct-02	Opioid Dependence	0.00%	$0.02
14.	VFEND®	PO	24-May-02	Fungal Infection	0.00%	$0.02
15.	FOCALIN®	PO	13-Nov-01	Attention-Deficit Hyperactivity Disorder	0.00%	$0.01
16.	AVANDAMET®	PO	10-Oct-02	Diabetes	0.00%	$0.01
17.	NUVARING®	VG	3-Oct-01	Contraception	0.00%	$0.01
18.	ABILIFY®	PO	15-Nov-02	Psychosis	0.00%	$0.01
19.	NOVOLOG MIX 70/30®	SQ	1-Nov-01	Diabetes	0.00%	$0.01
20.	FASLODEX®	IM	25-Apr-02	Breast Cancer	0.00%	$0.00
	Top 20 New Drugs				0.81%	$4.72
	All New Drugs				0.87%	$5.07
	All Other Drugs				99.13%	$586.92
	All Drugs				**100.00%**	**$585.60**

PO - Oral; TP - Topical; SQ - Injected under the skin; TD - Transdermal; SL- Sublingual; VG - Vaginal; IM - Intramuscular

Only a couple of the products introduced in 2002 had a significant impact on total 2002 PMPY costs. Clarinex®, an active metabolite of Claritin® that is indicated for the treatment of allergies, was brought to market in early 2002. The patent for Claritin® expired in December 2002 and Claritin® is now available only in the OTC setting. In the period between the market entry of Clarinex® and the patent expiration date of Claritin®, the manufacturer attempted to convert Claritin® users to Clarinex®. These efforts resulted in a Clarinex® market share of 9.3 percent, despite its being on the market for only about three-quarters of the year; in contrast, Claritin® lost 11.2 percentage points in market share between 2001 and 2002. Because of the late date in the plan year that OTC Claritin® and other OTC loratadine products came to market, few plan sponsors changed their coverage rules for the antihistamine class. For the 2004 plan year, individual plan sponsors may choose to stop coverage of prescription antihistamine products, charge a higher copayment for those prescription products, cover the OTC products or adopt some combination of these options.

Bextra® (valdecoxib) is a COX-2 inhibitor used for the treatment of pain and inflammation. Although it does not appear to have a clear clinical advantage compared to the other COX-2 inhibitors (Vioxx® and Celebrex®), Bextra® may offer an additional therapeutic alternative when a COX-2 inhibitor is

appropriate as well as for those who cannot tolerate or do not receive an adequate response from the other COX-2 inhibitors. Despite being introduced several months into the year, Bextra® still managed to capture a 4.6 percent market share in the anti-rheumatics (NSAID) class.

Lexapro® (escitalopram) is a refined version of Celexa® (citalopram), used for the treatment of depression. The product was brought to market as Celexa® nears patent expiration in January 2004.

Zetia® (ezetimibe) is the first in a new class of cholesterol-lowering medications that blocks the absorption of cholesterol from the gastrointestinal tract. It may be used alone or in combination with a statin to help attain target cholesterol levels. Zetia® provides another treatment option for individuals who cannot tolerate or achieve cholesterol goals with other therapies. This drug is also being studied as a combination product with a statin as a single, once-daily dosage form for the treatment of high cholesterol. Additional cholesterol reducing products introduced in 2002 include Advicor® and Altocor®. Both of these products contain the statin drug lovastatin, and they were marketed after a key patent for Mevacor® (lovastatin) expired in December 2001. Advicor® combines long-acting niacin with lovastatin, while Altocor® is an extended-release lovastatin formulation to allow for once-daily dosing at all approved strengths.

Abilify® (aripiprazole) represents another option for the treatment of schizophrenia, especially for those who are resistant to or cannot tolerate current therapies. Because it was approved in November 2002, its impact on the 2002 drug trend is minimal.

Humira® (adalimumab) is another biologic TNF-alpha blocker used to treat rheumatoid arthritis. This product requires a self-administered subcutaneous injection once every other week. It will compete with current biologic agents, Enbrel® and Kineret™. The future growth of this class will be due to expanded indications for TNF-alpha blockers for the treatment of other diseases (e.g., psoriasis and ankylosing spondylitis, which is rheumatoid arthritis of the spine). Because Humira® was approved on the last day of 2002, it did not impact the 2002 drug trend.

Despite the low number of new drug approvals over the last several years, the impact of drugs brought to market during the past 11 years contributed significantly to 2002 PMPY costs. As shown in Figure 8 and Table 9, new drugs generally peak in cost impact 5 or 6 years after reaching the market — provided that they have patent life remaining. Moreover, the cumulative magnitude of the cost impact from new products depends on whether or not they grow into blockbusters. Thus, the effect of blockbuster drugs introduced in 1992, 1995 and 1997 in particular accounted for a significant portion of 2002 PMPY costs. After reaching maximum cost impact in 1997, drugs brought to market in 1992 still accounted for 8 percent of 2002 costs, primarily driven by the contributions of Zoloft®, Zocor®, Norvasc® and Zithromax®. Drugs introduced in 1995 contributed 9.1 percent to 2002 PMPY ingredient costs, the most of any year of introduction and at a level that has remained constant since 2000. Key products introduced in that year include Prevacid®, Glucophage®, Prempro® and Ultram®. The contribution made to 2002 costs remained substantial despite the lower cost associated with the generic versions of Glucophage® and Ultram® that went generic in 2002. Drugs introduced in 1997 contributed 9 percent to overall 2002 PMPY ingredient costs — including 4.7 percent contributed by Lipitor®, the key product introduced in 1997. Other key drugs introduced in that year were Levaquin®, Diovan® and Topamax®.

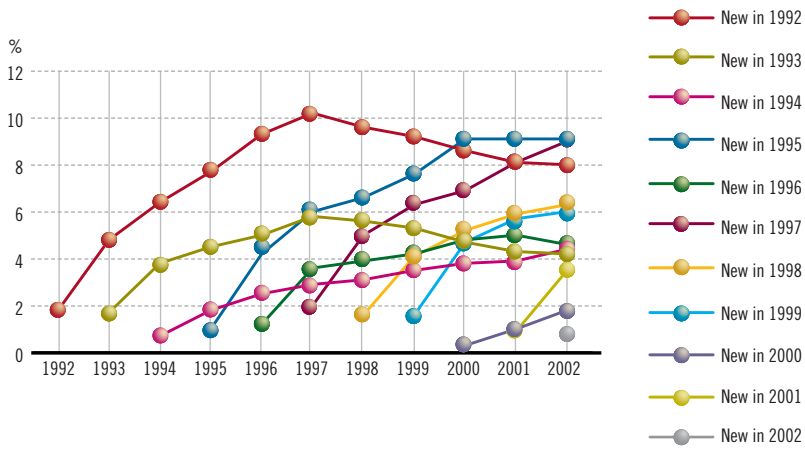
Table 9

Percent of 2002 Ingredient Cost and Cost Per Prescription for the Top 50 New Drugs Introduced Since 1992

RANK	BRAND NAME	YEAR OF INTRODUCTION	% 2002 COST	2002 COST/Rx
1.	LIPITOR®	1997	4.65%	$75.49
2.	PREVACID®	1995	2.85%	$128.69
3.	ZOCOR®	1992	1.84%	$106.04
4.	CELEBREX®	1999	1.59%	$95.77
5.	NEXIUM®	2001	1.58%	$120.59
6.	ZOLOFT®	1992	1.55%	$75.40
7.	PAXIL®	1993	1.51%	$79.86
8.	CLARITIN®	1993	1.37%	$78.77
9.	VIOXX®	1999	1.20%	$78.70
10.	ALLEGRA®	1996	1.15%	$60.61
11.	EFFEXOR®	1994	1.09%	$98.31
12.	NORVASC®	1992	1.07%	$47.71
13.	CELEXA®	1998	1.00%	$67.22
14.	GLUCOPHAGE®	1995	0.98%	$46.61
15.	NEURONTIN®	1994	0.89%	$115.44
16.	FOSAMAX®	1995	0.89%	$60.30
17.	ACTOS®	1999	0.86%	$132.43
18.	ZITHROMAX®	1992	0.84%	$37.63
19.	SINGULAIR®	1998	0.80%	$76.72
20.	ZYRTEC®	1996	0.79%	$50.40
21.	ROXICODONE™	1992	0.71%	$188.10
22.	AVANDIA®	1999	0.69%	$110.23
23.	AMBIEN®	1993	0.67%	$60.09
24.	HYZAAR®	1995	0.65%	$48.53
25.	PLAVIX®	1998	0.65%	$103.64
26.	IMITREX®	1995	0.63%	$178.67
27.	PREMPRO™	1995	0.59%	$28.96
28.	AVONEX® ADMINISTRATION PACK	1996	0.59%	$906.28
29.	PROTONIX®	2000	0.57%	$94.32
30.	FLONASE®	1994	0.56%	$55.45
31.	ACIPHEX®	1999	0.55%	$119.69
32.	REBETOL®	2001	0.54%	$1,347.76
33.	ENBREL®	1998	0.53%	$1,105.15
34.	LEVAQUIN®	1997	0.53%	$79.59
35.	LOTREL®	1995	0.45%	$61.55
36.	PEG-INTRON®	2001	0.45%	$1,086.35
37.	EVISTA®	1998	0.39%	$63.76
38.	ACCUTANE®	1992	0.38%	$413.18
39.	DIOVAN®	1997	0.37%	$43.30
40.	VIAGRA®	1998	0.36%	$54.42
41.	ASACOL®	1992	0.35%	$166.87
42.	FLOVENT®	1996	0.35%	$71.73
43.	BIPHETAMINE®	1992	0.35%	$71.20
44.	VALTREX®	1995	0.34%	$100.05
45.	NASONEX®	1997	0.34%	$57.45
46.	LAMISIL®	1996	0.34%	$221.65
47.	TOPAMAX®	1997	0.34%	$162.22
48.	RISPERDAL®	1994	0.33%	$149.97
49.	CLARINEX®	2002	0.33%	$56.73
50.	TRICOR®	1998	0.32%	$64.26
	OTHER		57.27%	$40.72
	Total		**100.00%**	**$82.31**

Figure 8

Percent of Ingredient Cost Accounted for by New Drugs Introduced Since 1992



Drugs introduced in 1998 and 1999 contributed about 6 percent to 2002 costs, and their respective contributions continue to grow. Key products introduced in 1998 include Celexa®, Singulair®, Enbrel®, Plavix®, Evista® and Viagra®. The dollar impact of drugs introduced in 1999 on 2002 costs is concentrated in a few products. Celebrex® and Vioxx® accounted for 2.8 percent of 2002 costs, with Actos® and Avandia® contributing 1.5 percent to these costs. In contrast, drugs brought to market in 2000 contributed a minimal 1.8 percent to 2002 costs, with the only significant drug introduced in that year being Protonix®. A few new products introduced in 2001 accounted for a significant percentage of 2002 costs. These products, Nexium®, PEG-Intron® and Rebetol®, together contributed 2.9 percent to 2002 costs, and they are expected to have a greater impact in 2003.

Over the next several years, the number of new drugs potentially entering the marketplace is similar to levels seen in the recent past. According to SG Cowen[30], 1,084 products are in the development pipeline, compared with 1,050 and 1,010 for the previous two years, respectively. Of these products, 212 are in preclinical study, 743 are in phase I, II or III clinical trials, and the applications for another 129 have been filed with the FDA. These numbers were 191, 707 and 152, respectively, for the previous year. However, few blockbusters are expected to result from this pipeline in the near future.

30 SG Cowen Securities. *Pipeline Pulse.* October 2002.

Summary

PMPY ingredient costs increased by 18.5 percent to $585.60 in 2002. It should again be noted that this year's Report expresses PMPY ingredient costs as AWP less 12 percent for brands and AWP less 36 percent for generics. In contrast, previous editions of the Report considered ingredient costs as full AWP costs. More than 60 percent of this rise was due to higher per prescription costs, 34.2 percent was attributable to increased utilization and 5.3 percent to medicines brought to market in 2002. The inflation rate grew by 7.5 percent, accounting for 43.4 percent of the overall 2001-2002 PMPY expenditure increase. A little more than one-half of the utilization increase is due to more prescriptions per utilizer and the remainder to more members using prescription drugs.

The magnitude of the 2002 PMPY ingredient cost for a given class generally translates into the proportion of total PMPY costs attributable to that class. The top five therapy classes in terms of costs (gastrointestinals, antihyperlipidemics, antidepressants, antihypertensives and NSAIDs) accounted for 36.8 percent of total 2002 PMPY costs and 39.6 percent of the 2001-2002 cost increase. PMPY costs for the next five classes (antidiabetics, antiasthmatics, antihistamines, antivirals and dermatologicals) represented another 17.1 percent of the overall 2002 PMPY costs and 18.3 percent of the 2001-2002 growth (see Table 10). The overlap between the top 14 classes in terms of 2002 PMPY costs and 2001-2002 cost change is also quite substantial. With only one exception — dermatologicals, which ranked 10th in 2002 costs and 27th in contributing to 2001-2002 cost increases — the top 14 ranked classes on one measure were in the top 14 on the other scale.

Table 10
Top 10 Therapy Classes Contributing to 2002 Trend
Ranked by Percent of 2002 Trend Increase

THERAPY CLASS	2002 $ PMPY	2002 % TREND INCREASE
Gastrointestinals	$53.60	11.9%
Antihyperlipidemics	$51.77	10.9%
Antidepressants	$50.46	8.7%
Antihypertensives	$30.97	5.0%
Anti-Rheumatic (NSAIDs)	$28.66	3.2%
Antidiabetics	$25.66	3.6%
Antiasthmatics	$22.27	4.5%
Antihistamines	$21.69	4.2%
Antivirals	$15.59	5.2%
Dermatologicals	$15.05	0.7%
Other	$269.86	42.1%
Total	$585.60	100.0%

Just as drug costs are concentrated in relatively few therapy classes, so too are they concentrated among a relatively small number of members. About 58.7 percent of eligible members used the pharmacy benefit in 2002, up from 57.4 percent in 2001. One-third of members used more than one prescription per month, and 11 percent used more than three prescriptions per month. When only the 58.7 percent of members who utilize the pharmacy benefit are considered, fully one-third spend less than $100 per year, whereas 14 percent spend more than $1,500 per year. Moreover, 5 percent of members accounted for 50.7 percent of total ingredient costs, and 10 percent of members accounted for 69.7 percent of ingredient costs.

2003-2007 Drug Cost Trend Forecast

The 18.5 percent increase in PMPY ingredient costs between 2001 and 2002 is the largest annual increase since Express Scripts began monitoring drug trends. It is also higher than the 15.9 percent trend that was predicted in last year's Report. One reason for this discrepancy is the actual 7.5 percent inflation rate versus the 6 percent that was expected. The higher-than-expected inflation rate was particularly evident in the antihistamine, cough/cold and decongestant classes. Last year's projections also underestimated utilization in a couple of key therapeutic classes. For example, PMPY use of proton pump inhibitors was anticipated to grow by 15 percent, but use actually rose by over 24 percent. Similarly, antidepressant and hypnotic utilization grew 16.4 percent and 12.4 percent, respectively, in contrast to their expected 12 percent and 7 percent growth rates. Driven primarily by changes in plan sponsor coverage rules, the use of oral contraceptives also grew faster than expected. One class that grew much faster than projected was antivirals. PMPY cost increases in this class accounted for more than 5 percent of the total PMPY growth in 2002. PMPY cost growth for drugs used to treat hepatitis rose by a substantial 168 percent, driven primarily by the increased use of expensive products like PEG-Intron® and Rebetol®.

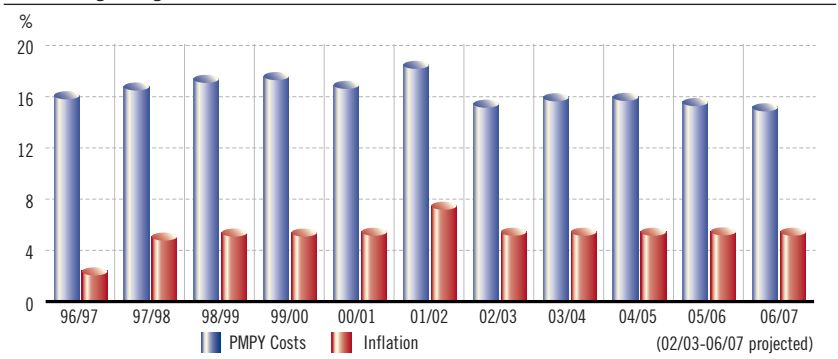
In the remainder of this section, Express Scripts' annual projections for the next 5 years are presented both in the aggregate and for major therapy class groupings. In terms of the former, Express Scripts projects that PMPY ingredient costs will continue to rise but at a reduced and relatively stable rate through 2007. More specifically, Express Scripts projects that drug costs will grow by:

- 15.5 percent in 2003
- 16.0 percent in 2004
- 16.0 percent in 2005
- 15.6 percent in 2006
- 15.2 percent in 2007

These annual projected growth rates translate into PMPY ingredient costs growing by 107 percent over the next 5 years from $585.60 in 2002 to $1,212.45 in 2007. Inflation, a key component of overall trend, is projected to grow at 5.5 percent annually through 2007. The relationship between our overall PMPY cost projections and our inflation assumptions is depicted graphically in Figure 9.

Figure 9

Percent Changes in Ingredient Costs From 1996-1997 to 2006-2007



In addition to inflation, other factors in the therapy class specific projections are the aging of the population, anticipated utilization and product mix, introduction of new products and products losing patent status. Express Scripts' annual PMPY cost estimates from 2003 through 2007 are presented in the aggregate and for major therapeutic classes, along with a brief rationale for these projections in Table 11. The remainder of this section presents the major new products anticipated to be marketed and the branded products scheduled to lose patent protection between 2003 and 2007.

Table 11
2001-2002 Summary and 2003-2007 Forecast for Major Therapy Classes

THERAPY CLASS	2001 $PMPY	% CHANGE	2002 $PMPY	% EST. CHANGE	2003 EST. $PMPY
Gastrointestinal	**$42.75**	**25.4%**	**$53.60**	**15.2%**	**$61.72**
PPIs	$35.41	31.98%	$46.73	20.5%	$56.31
Utilization expected to increase at somewhat lower rates. Competition among generic omeprazole manufacturers hard to predict.					
H2s	$6.18	-9.70%	$5.58	-3.0%	$5.42
Utilization will continue to shift to PPIs and OTC products.					
Central Nervous System (CNS)	**$68.60**	**20.5%**	**$82.65**	**19.3%**	**$98.58**
Antidepressants	$42.51	18.7%	$50.46	18.5%	$59.80
New indications for existing products will drive up utilization; new brand products will partially offset cost impact of generic Prozac®, Celexa® and Wellbutrin SR®.					
Anticonvulsants	$10.68	33.5%	$14.26	25.5%	$17.90
Use of newer products for epilepsy and use of Neurontin® and its successor pregabalin for pain relief will drive up costs.					
Antianxiety Agents	$6.34	1.6%	$6.44	8.5%	$6.98
This mostly generic class will experience moderate growth.					
Antipsychotics	$5.47	26.9%	$6.94	22.5%	$8.50
Introduction of Abilify® and expanded uses for existing products will drive up costs.					
Hypnotics	$3.61	26.3%	$4.56	18.5%	$5.40
Next generation of hypnotics expected to come to market and will drive use of this class.					
Cardiovascular	**$51.57**	**12.7%**	**$58.10**	**10.9%**	**$64.42**
Antihyperlipidemics	$41.83	23.8%	$51.77	20.5%	$62.39
Utilization expected to continue high growth rates; cost effect of upcoming generics will be somewhat mitigated by new brand products in 2006-2007.					
Antihypertensives	$26.41	17.3%	$30.97	13.0%	$35.00
More ACE inhibitors going generic but utilization will continue at high levels.					
Calcium Blockers	$13.57	1.2%	$13.73	3.5%	$14.21
Declining use of class expected.					
Beta Blockers	$8.80	19.6%	$10.53	15.0%	$12.10
Continued important role of generic-dominated class in treatment of hypertension and heart failure.					
Diuretics	$2.79	3.3%	$2.88	8.0%	$3.11
Recent ALLHAT findings support first-line use for hypertention.					
Pain/Inflammation	**$45.04**	**15.2%**	**$51.90**	**14.6%**	**$59.48**
Anti-Rheum (NSAIDs)	$10.81	0.19%	$10.83	4.5%	$11.32
Expect stable use of generic NSAIDs, but more use of DMARDs (Enbrel®, Humira™ and Remicade™) will drive up cost per prescription.					
COX-2s	$14.91	19.57%	$17.82	15.5%	$20.59
Use of this class will be pretty stable over the period.					
Narcotic Analgesics	$12.30	21.9%	$14.99	19.5%	$17.92
Utilization growth will moderate, but somewhat greater use of expensive products will drive costs up.					
Migraine Products	$7.03	17.4%	$8.25	17.0%	$9.65
Increased use of prophylactic agents will cause significant class growth.					
Diabetes	**$22.39**	**14.6%**	**$25.66**	**18.7%**	**$30.46**
Oral	$18.24	10.22%	$20.11	17.5%	$23.63
Use will remain stable, and mix is expected to grow from greater use of more expensive products.					
Insulin	$4.14	34.04%	$5.55	23.0%	$6.83
Use of more expensive insulins will drive cost increases.					

Table 11 continued on the following page.

% EST. CHANGE	2004 EST. $PMPY	% EST. CHANGE	2005 EST. $PMPY	% EST. CHANGE	2006 EST. $PMPY	% EST. CHANGE	2007 EST. $PMPY
18.4%	**$73.10**	**19.8%**	**$87.59**	**18.2%**	**$103.56**	**16.6%**	**$120.70**
20.5%	$67.85	21.5%	$82.44	19.5%	$98.51	17.5%	$115.75
-3.0%	$5.25	-2.0%	$5.15	-2.0%	$5.04	-2.0%	$4.94
19.3%	**$117.55**	**18.1%**	**$138.77**	**17.0%**	**$162.33**	**16.6%**	**$189.28**
18.5%	$70.86	16.5%	$82.56	14.5%	$94.53	13.5%	$107.29
25.5%	$22.46	25.5%	$28.19	25.5%	$35.37	25.5%	$44.39
7.5%	$7.51	7.5%	$8.07	7.5%	$8.68	7.5%	$9.33
21.5%	$10.33	20.5%	$12.44	20.5%	$14.99	20.5%	$18.07
18.5%	$6.40	17.5%	$7.52	16.5%	$8.76	16.5%	$10.21
12.6%	**$72.54**	**13.6%**	**$82.42**	**14.4%**	**$94.26**	**14.7%**	**$108.07**
20.5%	$75.18	19.5%	$89.84	18.5%	$106.46	17.5%	$125.09
16.0%	$40.60	17.5%	$47.70	18.5%	$56.53	18.5%	$66.98
3.5%	$14.70	3.5%	$15.22	3.5%	$15.75	3.5%	$16.30
14.5%	$13.86	14.0%	$15.80	13.5%	$17.93	13.5%	$20.35
8.5%	$3.37	9.5%	$3.70	9.5%	$4.05	9.5%	$4.43
14.9%	**$68.31**	**14.6%**	**$78.30**	**14.5%**	**$89.65**	**14.3%**	**$102.51**
6.5%	$12.06	6.5%	$12.84	7.5%	$13.80	8.5%	$14.98
15.5%	$23.78	15.5%	$27.46	15.5%	$31.72	15.5%	$36.64
18.5%	$21.23	17.5%	$24.95	16.5%	$29.06	15.5%	$33.57
16.5%	$11.25	16.0%	$13.04	15.5%	$15.07	15.0%	$17.33
18.3%	**$36.03**	**17.8%**	**$42.46**	**17.6%**	**$49.94**	**17.6%**	**$58.73**
17.5%	$27.76	17.5%	$32.62	17.5%	$38.33	17.5%	$45.04
21.0%	$8.27	19.0%	$9.84	18.0%	$11.61	18.0%	$13.70

Table 11
2001-2002 Summary and 2003-2007 Forecast for Major Therapy Classes

THERAPY CLASS	2001 $PMPY	% CHANGE	2002 $PMPY	% EST. CHANGE	2003 EST. $PMPY
Respiratory	**$51.71**	**20.0%**	**$62.05**	**15.3%**	**$71.57**
Antiasthmatics	$18.13	22.8%	$22.27	19.0%	$26.51
Utilization will continue to grow and the use of more expensive products (Singulair®, Pulmicort® and Advair Diskus®) will lead to double-digit growth.					
Antihistamines	$17.89	21.2%	$21.69	16.0%	$25.16
Utilzation and mix difficult to project given uncertainty over plan sponsor OTC coverage rules.					
Cough/Cold	$8.53	13.6%	$9.69	10.5%	$10.71
Utilzation and mix difficult to project given uncertainty over plan sponsor OTC coverage rules.					
Decongestants/Nasal Steroids	$7.15	17.4%	$8.40	9.5%	$9.20
Growth will moderate with few expected new products.					
Dermatologicals	**$14.37**	**4.7%**	**$15.05**	**11.0%**	**$16.71**
Price increases will drive class costs.					
Antivirals	**$10.52**	**43.1%**	**$15.06**	**21.7%**	**$18.32**
HIV	$5.15	5.82%	$5.45	9.5%	$5.96
New, expensive drug introductions in 2003 will increase per prescription costs.					
Herpes	$3.14	15.06%	$3.61	12.0%	$4.04
Modest growth will continue.					
Hepatitis	$2.24	168.16%	$6.00	38.5%	$8.31
Utilization growth will continue but will moderate over time.					
Women's Health	**$32.33**	**12.9%**	**$36.51**	**13.5%**	**$41.45**
Estrogens	$11.62	-5.0%	$11.04	-0.5%	$10.98
Utilization will continue to decline in 2003 and then will remain relatively stable.					
Oral Contraceptives	$8.91	19.6%	$10.65	13.5%	$12.09
Cost growth primarily driven by expected wider coverage of OCs by plan sponsors.					
Misc. Endocrine	$11.80	25.6%	$14.82	24.0%	$18.38
The aging of the population, massive undertreatment of osteoporosis in women and men, and fear of using estrogens will lead to substantial utilization growth.					
Anti-infectives	**$27.35**	**2.8%**	**$28.11**	**5.9%**	**$29.76**
Macrolides	$7.52	-0.4%	$7.48	1.0%	$7.56
Price increases will be primary factor in overall class cost growth.					
Cephalosporins	$5.55	0.4%	$5.57	-0.5%	$5.54
Class dominated by generics and use expected to decline.					
Penicillins	$7.21	2.0%	$7.36	5.5%	$7.76
Class dominated by generics and use expected to decline.					
Quinolones	$7.08	8.8%	$7.70	15.5%	$8.89
Class costs will escalate as utilization increases substantially.					
Subtotal	**$408.46**	**17.6%**	**$480.48**	**15.5%**	**$554.85**
Other	$85.74	22.6%	$105.12	15.5%	$121.39
Total	**$494.20**	**18.5%**	**$585.60**	**15.5%**	**$676.24**

% EST. CHANGE	2004 EST. $PMPY	% EST. CHANGE	2005 EST. $PMPY	% EST. CHANGE	2006 EST. $PMPY	% EST. CHANGE	2007 EST. $PMPY
13.5%	**$81.24**	**12.6%**	**$91.44**	**12.3%**	**$102.69**	**11.6%**	**$114.60**
17.5%	$31.15	15.5%	$35.97	15.5%	$41.55	13.5%	$47.16
14.5%	$28.81	13.5%	$32.70	12.5%	$36.79	12.5%	$41.38
6.5%	$11.40	6.5%	$12.14	6.5%	$12.93	6.5%	$13.77
7.5%	$9.89	7.5%	$10.63	7.5%	$11.43	7.5%	$12.28
11.0%	**$18.55**	**11.0%**	**$20.59**	**11.0%**	**$22.85**	**11.0%**	**$25.37**
20.8%	**$22.14**	**18.5%**	**$26.24**	**15.6%**	**$30.34**	**12.9%**	**$34.25**
9.5%	$6.53	8.5%	$7.08	7.5%	$7.62	6.5%	$8.11
11.5%	$4.51	11.0%	$5.00	10.5%	$5.53	10.5%	$6.11
33.5%	$11.10	27.5%	$14.15	21.5%	$17.19	16.5%	$20.03
15.2%	**$47.73**	**16.5%**	**$55.60**	**17.8%**	**$65.49**	**18.6%**	**$77.67**
3.0%	$11.31	4.0%	$11.76	5.0%	$12.35	6.0%	$13.09
13.5%	$13.72	13.5%	$15.57	13.5%	$17.68	13.5%	$20.06
23.5%	$22.70	24.5%	$28.26	25.5%	$35.47	25.5%	$44.51
5.8%	**$31.49**	**6.4%**	**$33.51**	**7.1%**	**$35.88**	**7.5%**	**$38.55**
1.0%	$7.63	1.0%	$7.71	1.0%	$7.79	1.0%	$7.87
0.5%	$5.57	0.5%	$5.60	0.5%	$5.63	0.5%	$5.66
5.5%	$8.19	5.5%	$8.64	5.5%	$9.12	5.5%	$9.62
13.5%	$10.09	14.5%	$11.55	15.5%	$13.34	15.5%	$15.41
16.0%	**$643.86**	**16.0%**	**$746.74**	**15.6%**	**$863.45**	**15.2%**	**$994.81**
16.0%	$140.86	16.0%	$163.37	15.6%	$188.90	15.2%	$217.64
16.0%	**$784.72**	**16.0%**	**$910.11**	**15.6%**	**$1,052.35**	**15.2%**	**$1,212.45**

New Products Expected to Come to Market Between 2003 and 2007

Gastrointestinal (GI)

Biologic products will begin to make a greater impact in the treatment of Crohn's disease. Antegren® is a humanized monoclonal antibody designed to bind to receptors on white blood cells, altering their response to and involvement in the inflammatory process. This drug is being studied for a variety of diseases with an inflammatory component, including Crohn's disease and multiple sclerosis (MS). Humicade™, a monoclonal antibody that blocks the effects of Tumor Necrosis Factor alpha (TNF-alpha), is also under investigation for the treatment of both Crohn's disease and rheumatoid arthritis (RA). Once approved, these agents will compete with Remicade®, which is currently the only biologic agent approved for the treatment of Crohn's disease.

In 2002, the FDA approved the marketing of Zelnorm® and the re-introduction of Lotronex® for the treatment of irritable bowel syndrome (IBS). However, with approximately 50 million Americans believed to suffer from IBS, its treatment remains a relatively untapped market. Dexloxiglumide and renzapride are being studied for the treatment of constipation-predominant IBS, while cilansetron is being evaluated for the treatment of the diarrhea-predominant type of the disease. The FDA may be cautious with the approval of these products following the withdrawal and eventual re-introduction of Lotronex®.

Emend® is a substance p inhibitor for the treatment of chemotherapy-induced nausea and vomiting. Clinical trials have indicated that when used in combination with other anti-emetics, Emend® may be effective for the treatment of both acute and delayed nausea and vomiting. If FDA review proceeds as planned, this drug should reach the market in 2003.

			EXPECTED RELEASE DATE				
BRAND NAME	**GENERIC NAME**	**PROPOSED USE**	**2003**	**2004**	**2005**	**2006**	**2007**
Antegren®	natalizumab	Crohn's disease		x			
Emend®	aprepitant	Nausea, vomiting	x				
	dexloxiglumide	IBS			x		
	cilansetron	IBS			x		
	renzapride	IBS					x
Humicade™	CDP-571	Crohn's disease		x			

Patent Expirations:
- Zofran® 2005
- Protonix® 2006 (extension likely)

Central Nervous System (CNS)

In 2003, three additional medications for the treatment of erectile dysfunction (ED) may enter the U.S. prescription market. Cialis® and Levitra®, oral medications that are currently under FDA review, have a mechanism of action similar to Viagra®. However, they are more selective for the phosphodiesterase 5 enzyme (which may result in fewer side effects), and they have a longer duration of action. Uprima® is a dopamine receptor agonist that is administered sublingually (under the tongue). Since it has a different mechanism of action, it has the potential to work in patients who are unresponsive to the other therapies.

The treatment of depression is another significant focus for medication development. Cymbalta® is a norepinephrine and serotonin re-uptake inhibitor for the treatment of depression and, at a different dose, for the treatment of stress urinary incontinence. Gepirone ER is a 5-HT1a agonist for the treatment of major depression and major depression with anxiety. However, the FDA is requiring additional studies to support marketing approval, delaying potential approval until at least 2004. Aprepitant is also being studied as an antidepressant, but limited efficacy data are available at this time.

The sedative/hypnotic market will see some additional growth in the upcoming years. Estorra™ is under development for the treatment of transient and chronic insomnia. It is an isomer of zopiclone, a hypnotic agent available only outside of the U.S. Indiplon is a GABA agonist/non-benzodiazepine sedative/hypnotic for treatment of chronic insomnia. It is being looked at in both rapid-release and modified-release formulations to help initiate and maintain sleep.

Pregabalin is a follow-on compound to Neurontin®. It is being studied for many diseases, including epilepsy, general anxiety disorder (GAD) and neuropathic pain. Development of this drug was temporarily delayed due to concerns about carcinogenicity in animal studies.

			EXPECTED RELEASE DATE				
BRAND NAME	**GENERIC NAME**	**PROPOSED USE**	**2003**	**2004**	**2005**	**2006**	**2007**
Cymbalta®	duloxetine	Depression, urinary incontinence	x				
Cialis®	tadalafil	Erectile dysfunction	x				
Levitra®	vardenafil	Erectile dysfunction	x				
Uprima®	apomorphine	Erectile dysfunction	x				
	memantine	Alzheimer's disease		x			
Zomaril™	iloperidone	Psychosis		x			
Estorra™	eszopiclone	Hypnotic		x			
	pregabalin	Epilepsy, GAD, neuropathic pain			x		
	rimonabant	Obesity			x		
	gepirone ER	Depression		x			
	aprepitant	Depression			x		
	Org-5222	Psychosis					x
	indiplon	Hypnotic			x		

Patent Expirations:

- Neurontin® key patent expired (ongoing litigation), competition possible 2003
- Wellbutrin SR®/Zyban® patent expired (generics awaiting appellate ruling/FDA approval)
- Serzone® 2003
- Paxil® 2003 (ongoing litigation)
- Celexa® 2004
- Zoloft® 2006
- Imitrex® 2007
- Ambien® 2007

Respiratory

Xolair™ is a monoclonal antibody that binds and inhibits the effects of IgE antibodies, which are immune system proteins involved in the inflammatory process that produces many symptoms of allergic asthma. This product may be limited to the treatment of severe, refractory asthma because it likely will require a monthly injection in a clinic setting. A product with a similar mechanism of action is TNX-901, which is being developed to provide protection against reactions to unintentional peanut ingestion by people who have severe allergies to peanuts.

With initiatives to comply with the Montreal Protocol by phasing out the use of all chlorofluorocarbons (CFCs), some of the currently available metered dose inhalers used to treat asthma eventually will be removed from the market. Therefore, the additional CFC-free products under development will increase therapeutic options for people with asthma. Ciclesonide and Asmanex® are both CFC-free inhaled corticosteroids for the maintenance treatment of asthma. Spiriva® is a longer-acting version of the drug in Atrovent®. Therapy with Spiriva® would require a once-daily administration, compared to four times a day with Atrovent®.

A new class of oral medications known as phosphodiesterase 4 (PDE4) inhibitors may provide anti-inflammatory and bronchodilatory effects for the treatment of asthma and chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis. Leading agents in this class include Ariflo® and roflumilast. Some physicians feel that these products may have only modest benefits over theophylline. However, their roles in the treatment of asthma and COPD have yet to be determined.

The non-sedating antihistamine class may see another addition in 2004, following the completion and analysis of additional safety studies for Soltara®. In March 2002, the FDA issued a "not approvable" letter for Soltara®, making its market entry date uncertain.

			EXPECTED RELEASE DATE				
BRAND NAME	**GENERIC NAME**	**PROPOSED USE**	**2003**	**2004**	**2005**	**2006**	**2007**
Spiriva®	tiotropium	COPD	x				
Xolair™	omalizumab	Allergic asthma	x				
Ariflo®	cilomilast	Asthma, COPD		x			
	ciclesonide	Asthma		x			
Asmanex®	mometasone	Asthma	x				
	roflumilast	Asthma, COPD			x		
Soltara®	tecastemizole	Allergies		x			
	TNX-901	Peanut allergies				x	

Patent Expirations

- Flovent® 2004
- Flonase® 2004
- Allegra® 2004 (pending court ruling)
- Zyrtec® 2007
- Clarinex® 2007

Pain/Inflammation

The marketing of biologic products for the treatment of psoriasis and psoriasis-related complications will increase disease awareness, expand treatment options and eventually transform treatment of this disease into the next multi-billion dollar market. Raptiva ™ is the next new biologic agent likely to receive approval for the treatment of psoriasis. However, look for the TNF inhibitors currently on the market (e.g., Enbrel®, Remicade® and Humira™) to seek approval for the treatment of psoriasis. In 2005, the growing class of TNF Inhibitors will see the introduction of CDP-870, which has the added convenience of once-a-month subcutaneous administration. Other agents for the treatment of rheumatoid arthritis (RA) include Tenovil™, a natural anti-inflammatory and immune system regulator; and pralnacasan, an orally active small molecule drug known as an ICE inhibitor (interleukin-1b converting enzyme inhibitor), a medication that may block the formation of key cytokines involved in the inflammation process.

Two additional COX-2 inhibitors will likely compete in this multi-billion dollar market in 2004. Submission of the new drug application (NDA) for Arcoxia™ with data to support its use in ankylosing spondylitis (RA of the spine) is anticipated in mid-2003, placing its final approval sometime in 2004. The NDA for Prexige® was submitted to the FDA in 2002, but an additional clinical trial will be required to support approval, delaying final approval until at least 2004. It is unclear if these agents will offer any clinical advantages in the COX-2 inhibitor class, or only compete for a share of the market.

Antegren®, a humanized monoclonal antibody, is one of the first in a new class of alpha 4 integrin inhibitors that prevent the migration of inflammatory cells from blood vessels to sites of inflammation. Antegren® is being studied for the treatment of inflammatory diseases, including Crohn's disease and multiple sclerosis (MS).

			EXPECTED RELEASE DATE				
BRAND NAME	**GENERIC NAME**	**PROPOSED USE**	**2003**	**2004**	**2005**	**2006**	**2007**
Raptiva®	efalizumab	Psoriasis	x				
Prexige®	lumiracoxib	Arthritis, pain		x			
	CDP-870	RA			x		
Tenovil™	IL-10	RA			x		
Antegren®	natalizumab	MS		x			
Arcoxia™	etoricoxib	Arthritis, pain		x			
	pralnacasan	RA				x	
Humira™	adalimumab	Arthritis			x		

Patent Expirations

- Duragesic® 2005
- OxyContin® 2007

Cardiovascular

As the patents on several key cholesterol-lowering products begin to approach expiration, manufacturers are working to develop novel therapies for modifying cholesterol levels (raising HDL or lowering total cholesterol, LDL and triglycerides). The next entrants to the "statin" market likely will be Crestor® in late 2003, followed by pitavastatin in 2006. Avasimibe is an ACAT (acyl-coenzyme A: cholesterol acyltransferase) inhibitor that may prevent the progression of atherosclerosis as well as lower cholesterol. CP-529,414 is a cholesterol ester transfer protein (CETP) inhibitor to be used in combination with Lipitor® to elevate HDL cholesterol and lower LDL cholesterol.

Lercanidipine is a calcium blocker anticipated to compete with Norvasc® for the treatment of hypertension. Although an NDA for lercanidipine was submitted in 2001, the FDA is requiring additional clinical trials prior to granting full approval.

Exanta™ is a novel, orally-administered thrombin inhibitor for the prevention of venous thromboembolisms in orthopedic surgery. If approved, this drug is likely to compete with the low-molecular-weight heparins and Coumadin®. Dronedarone is an antiarrhythmic medication similar to amiodarone. However, a recent study of this drug was discontinued following an interim analysis showing an excess risk of death in the treatment group. An in-depth analysis of the results will be required before a new study protocol is considered.

Conivaptan is a vasopressin (V1 and V2) receptor antagonist for treatment of hyponatremia (sodium deficiency) and CHF. Fasidotril, a vasopeptidase inhibitor, is another drug being studied for the treatment of congestive heart failure (CHF) and hypertension. If development of this drug continues as planned, it will help address the increased incidence of angioedema experienced with other vasopeptidase inhibitors (e.g., Vanlev™).

			EXPECTED RELEASE DATE				
BRAND NAME	**GENERIC NAME**	**PROPOSED USE**	**2003**	**2004**	**2005**	**2006**	**2007**
Crestor®	rosuvastatin	Dyslipidemia	x				
Exanta™	ximelagatran	Anticoagulant		x			
	lercanidipine	Hypertension				x	
	dronedarone	Arrhythmia			x		
	pitavastatin	Dyslipidemia				x	
	avasimibe	Dyslipidemia, atherosclerosis				x	
	CP-529,414	Dyslipidemia			x		
	conivaptan	Hyponatremia, CHF			x		
	fasidotril	Hypertension, CHF					x

Patent Expirations

- Accupril® 2003
- Monopril® 2003
- Lotensin® 2004
- Altace® 2005
- Pravachol® 2006
- Zocor® 2006
- Norvasc® 2007
- Coreg® 2007

Women's Health

Seasonale® is likely to enter the market in 2003. This novel oral contraceptive is taken continuously for 84 days, followed by a week of placebo to allow for a menstrual period. This would decrease the number of periods from 13 to 4 per year for women taking the drug. Physicians have been prescribing monophasic oral contraceptives in a similar manner for the treatment of endometriosis, severe dysmenorrhea and migraines that worsen during the menstrual period.

With the recent FDA-recommended labeling changes for estrogen-containing hormone replacement therapies (HRT), the use of non-estrogen products for the treatment and prevention of post-menopausal osteoporosis is likely to increase. Bazedoxifene and lasofoxifene are estrogen-receptor modulators under study for the prevention of postmenopausal osteoporosis. Bonviva® likely will be the next agent introduced to the bisphosphonate market. However, a once-weekly Bonviva® formulation probably will be required to compete with the market leaders. Xyvion® is a product that possesses weak estrogenic, progestogenic and androgenic properties. Its continued development may be questionable, due to the recent FDA-requested changes to estrogen products for use as HRT.

			EXPECTED RELEASE DATE				
BRAND NAME	**GENERIC NAME**	**PROPOSED USE**	**2003**	**2004**	**2005**	**2006**	**2007**
Seasonale®	ethinyl estradiol/ levonorgestrel	Oral contraceptive	x				
Bonviva®	ibandronate	Osteoporosis			x		
Xyvion®	tibolone	HRT				x	
	bazedoxifene	Osteoporosis, HRT				x	
	lasofoxifene	Osteoporosis, HRT			x		

Patent Expirations

- Nolvadex® 2003
- Ortho Tri-Cyclen® 2003
- Ortho-Novum® 7/7/7 2003
- Fosamax® 2008 (patent challenges pending)

Anti-Infectives

Fuzeon™, approved in March 2003, is the first drug in a new class of HIV medications. Known as viral fusion inhibitors, this class of drugs prevents HIV from binding to and "fusing" with healthy T-cells, preventing the healthy cells from becoming infected. Therapy with this drug will require a subcutaneous injection twice daily, and it will be used in combination with oral medications for HIV treatment. Also in development are other drugs with mechanisms of action similar to products currently available for the treatment of HIV. They include capravirine, atazanavir and fosamprenavir. These drugs may provide incremental benefits over the current drugs, but their true place in therapy has yet to be determined.

Ketolides are a new, emerging class of antibiotic drugs. Derivatives of macrolide antibiotics (e.g., erythromycin, clarithromycin), they have been shown to be effective against some strains of macrolide-resistant bacteria. With approval expected in 2003, Ketek® likely will be the first ketolide introduced in the U.S. Other antibiotics in development include garenoxacin, a broad spectrum quinolone; and oritavancin, a glycopeptide for the treatment of gram positive infections.

FluMist™ is an intranasal flu vaccine for the prevention of respiratory influenza. As with other influenza vaccines, it will be reformulated annually to reflect the currently circulating influenza A and B viruses. Initially, it likely will be limited for use in individuals from 5 to 49 years of age. A second intranasal influenza vaccine, FluINsure™, is currently in early clinical trials.

A couple of antifungal agents are in the near-term pipeline. Ravuconazole is a broad-spectrum antifungal with activity against most of the fungi that are responsible for severe infections in patients with or without a healthy immune system (e.g., aspergillosis, mucosal candidiasis, endemic mycosis and onychomycosis). The use of posaconazole, however, likely will be limited to severe infections in individuals with a compromised immune system (e.g., aspergillosis).

			EXPECTED RELEASE DATE				
BRAND NAME	**GENERIC NAME**	**PROPOSED USE**	**2003**	**2004**	**2005**	**2006**	**2007**
Fuzeon™	enfuvirtide	HIV	x				
FluMist™	influenza vaccine, intranasal	Influenza vaccine	x				
FluINsure™	influenza vaccine, intranasal	Influenza vaccine				x	
Ketek®	telithromycin	Antibiotic	x				
	garenoxacin	Antibiotic		x			
	atazanavir	HIV	x				
	fosamprenavir	HIV	x				
Noxafil®	posaconazole	Antifungal		x			
	oritavancin	Antibiotic			x		
	capravirine	HIV				x	
	ravuconazole	Antifungal				x	

Patent Expirations

- Cipro® 2003
- Rebetol® 2003
- Diflucan® 2004
- Biaxin® 2005
- Zithromax® 2005
- Cefzil® 2005
- Lamisil® 2007

Diabetes

A new class of injectable agents for the treatment of diabetes is beginning to emerge. Modeled after natural body chemicals known as glucagon-like peptide (GLP)-1, the new agents are being studied for their roles in regulating blood glucose. The furthest in development is Symlin™, followed by exendin-4 and NN-2211.

Insulin glulisine (HMR-1964) is a rapid-acting insulin analog similar to Novolog® and Humalog®. Insulin detemir is a long-acting basal insulin that provides less day-to-day variation in insulin levels than experienced with NPH. It will compete primarily with Lantus®. The development of the inhaled insulin, Exubera™ (dry powder insulin for inhalation), has been delayed significantly from its original projected timelines due to concerns about its long-term effects on pulmonary function.

LAF-237 is a dipeptidyl peptidase (DPP) IV inhibitor for treatment of type 2 diabetes. Initial findings from a study in patients with type 2 diabetes show that it may improve glucose tolerance and insulin response to oral glucose in patients with type 2 diabetes. Glitazones in development include balaglitazone, AZ-242 and KRP-297.

Diabetes care includes not only the maintenance of blood glucose but also the management of complications associated with the disease. Ruboxistaurin (formerly known as LY333531) is a protein kinase C beta inhibitor being developed for the treatment of diabetic neuropathy, proliferative retinopathy and macular edema. Sulodexide is a heparin-type molecule for treatment of diabetic nephropathy. Pregabalin, the follow-on to Neurontin®, is also being studied for the treatment of diabetic neuropathy.

			EXPECTED RELEASE DATE				
BRAND NAME	**GENERIC NAME**	**PROPOSED USE**	**2003**	**2004**	**2005**	**2006**	**2007**
Symlin™	pramlintide	Glucose regulation	x				
Exubera™	inhaled insulin	Diabetes		x			
	ruboxistaurin (LY333531)	Diabetes complications				x	
	balaglitazone	Oral antidiabetic				x	
	exendin-4 (AC2993)	Glucose regulation			x		
	pregabalin	Diabetic neuropathic pain			x		
	NN-2211	Glucose regulation				x	
	insulin glulisine	Insulin analog			x		
	insulin detemir	Insulin analog	x				
	sulodexide	Diabetes complications			x		
	KRP-297	Oral antidiabetic					x
	LAF-237	Oral antidiabetic				x	

Patent Expirations

- Glucophage® XR 2003
- Glucovance™ 2004
- Amaryl® 2005
- Actos® 2006

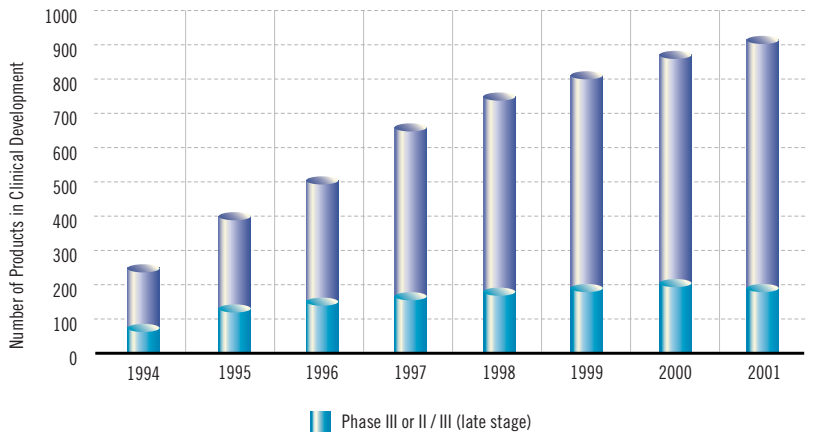
NOTES

The Growing Costs of Specialty Injectable Drug Products

Each year, more people use specialty injectable drugs as part of their medication therapy. In 2002, more people received specialty injectable products through their pharmacy benefits. This trend was clearly evident in Express Scripts' specialty-care pharmacy, which dispensed 90 percent more prescriptions in 2002 than in 2001.

U.S. revenues for the specialty pharmacy market, estimated at $22 billion in 2001, are expected to increase by 20 percent annually.[31] The expanding biotechnology industry is a significant driving force behind this growth. In 2001, over 900 products targeting more than 200 diseases were making their way through biotechnology drug company pipelines (see Figure 10).

Figure 10
Biotechnology Pipeline



Source: Goldman Sachs. Healthcare: Biotechnology. January 14, 2003: Page 8

Another factor driving growth of the injectable market is the lack of generic products. Although the FDA has an established process for approving generic equivalents of traditional drugs, the agency currently has no comparable process for allowing generic versions of biotech drugs to come to market.

With the typical injectable drug costing well over $1,000 per month, payers recognize the impact that specialty injectables can have on both medical and pharmacy benefits. The first step in addressing specialty drug cost is to establish a clear definition for this category. Currently, typical inclusion criteria include the annual drug cost, whether the product is injectable or infused, and whether it is administered in the home or a physician's office. Some plans also consider high-cost oral products, such as Tracleer® or Gleevec™, as specialty drugs.

31 Ransom J, Rettig T. Specialty Drug Distribution. Raymond James and Associates. July 16, 2002. Available at: http://170.12.99.3/researchpdf/IDRU071602RPT.PDF. Accessed March 25, 2003.

To manage the specialty cost effectively, a plan sponsor must consider drugs covered under both pharmacy and medical benefits. The medical benefit is of particular concern because of the unique coding structure used for medical claims. Drug-specific data is rarely available in medical claims; consequently, it is difficult for a plan to measure the drug spend or determine for which drugs they are paying. Many plans have begun moving these drugs to the pharmacy benefit, in part to determine their specialty drug cost. Others have created a new benefit called an "Injectable" benefit. Finally, others are looking for technological solutions to incorporate medical claims data and drug-specific information.

Today, the most common method of addressing the costs of specialty drugs is through discounted pricing via specialty pharmacies. These pharmacies often offer discounts in return for some promise of increased volume. Plans, on the other hand, must limit their members' choices in order to steer them to these providers. Specialty pharmacies frequently offer additional patient support through education and high-touch customer service. Specialty pharmacies have the ability to bill both pharmacy and medical benefits, yet plans struggle to consolidate the data across their network to measure total specialty cost.

Formularies have proven to be an effective way for plans to lower oral drug costs. Except in the class of growth hormones, however, only a few therapeutic substitutions now exist in the specialty drug category from which to build formularies and leverage manufacturer discounts. The drug pipeline shows several upcoming opportunities for competition to existing drugs, however. Plans should actively monitor these developing drugs in preparation for adopting specialty formularies.

Clinical programs, such as prior authorization and step therapy, can affect utilization for some specialty drugs. Drug therapies for RA, MS and hepatitis C all are candidates for these types of programs. Additionally, some patients may respond to disease management programs.

Increasingly, plans are looking to pharmacy benefit managers (PBMs) to help manage the specialty drug cost. PBMs have the ability to build networks of specialty pharmacies and leverage discounts. Additionally, PBMs can offer efficient, cost-effective mail service for certain specialty drugs. Overall, PBMs have proven tools and methods to lower plan costs. Finally, as PBMs address the issue of medical claims management, they will be in a position to integrate specialty drug data across both benefits, allowing for a complete management solution.

The following sections provide an overview of the top therapeutic classes that currently drive the injectable drug market. One notable exception is a general overview of cancer therapies, which contribute significantly to healthcare costs. While certain therapeutic classes related to cancer treatment can be found in this section of the Report, a more detailed discussion of cancer and its treatments can be found in Appendix A. It is important to note that the products mentioned in this section may be covered under either the medical or the pharmacy benefit, and in some cases, both.

Fertility Regulators

Primary Use: Infertility

Infertility is defined by the World Health Organization as the inability of a couple to achieve conception or bring a pregnancy to term after one year or more of regular, unprotected sexual intercourse. Primary infertility is the inability to conceive a first child and secondary infertility is the inability to conceive a second or subsequent child. One out of 10 couples worldwide experience primary or secondary infertility.[32] Infertility therapy is now highly successful, with pregnancy rates obtained with most treatment comparable to natural pregnancy rates.

Current drugs to treat infertility include chorionic gonadotropin (hCG), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Each of these drugs plays a specific role in the reproductive cycle. FSH stimulates the development of follicles in the ovaries, which ultimately lead to fully developed eggs. FSH is typically given with LH, which is responsible for final maturation of the developing egg; hCG triggers ovulation, so one of these products is given after FSH and LH have had time to work. Another class of products known as gonadotropin antagonists is used to control the ovulation cycle, which is important when exact timing is necessary for other infertility therapies.

Infertility treatments can be either human-derived or recombinant. Human-derived products are made from the urine of postmenopausal women, while recombinant products are produced using DNA technology. Most of the medications are self-injectable in nature. The following table lists some of the significant infertility products.

Table 12
Selected Infertility Products

DRUG NAME	PRODUCT TYPE	METHOD OF ADMINISTRATION
Gonal-f™	Recombinant FSH	Subcutaneous
Follistim®	Recombinant FSH	Subcutaneous
Pergonal®	Human-derived FSH/LH	Intramuscular
Repronex®	Human-derived FSH/LH	Subcutaneous
Lupron®	Gonadotropin antagonist	Intramuscular
Ovidrel®	Recombinant hCG	Subcutaneous
Antagon™	Gonadotropin antagonist	Subcutaneous
Bravelle™	Human-derived FSH	Subcutaneous
Cetrotide®	Gonadotropin antagonist	Subcutaneous

Pipeline: The pipeline for infertility drugs is relatively quiet. Most activity involves making existing products easier to take. The manufacturer of Gonal-f™ is developing a microencapsulated form of the drug that is designed to decrease the frequency of injections. Other companies continue to find ways to further purify their compounds, thereby reducing the risk of adverse reactions. Oral versions of these products are years away. Luveris®, which contains FSH and luteinizing hormone-releasing hormone (LHRH), is currently under review at the FDA.

32 Department of Reproductive Health and Research (RHR), World Health Organization. Infertility. October 2002. Available at: http://www.who.int/reproductive-health/infertility/index.htm. Accessed March 26, 2003.

Beta-interferons

Primary Use: Multiple Sclerosis

Multiple sclerosis (MS) is a progressive disease of the central nervous system. It is an autoimmune disease in which tissues surrounding the nerves of the body are damaged. This results in an inability of the nerves to communicate with one another, and leads to symptoms such as tremor, loss of balance and visual disturbances. MS has no cure.

There are four major types of MS: Relapsing-Remitting, Secondary-Progressive, Primary-Progressive and Progressive-Relapsing. Relapsing-Remitting MS is the most common form, occurring in approximately 75 percent of patients. This type of MS is characterized by intermittent attacks, or relapses, of MS symptoms followed by periods of near-normal functioning. About half of the patients with Relapsing-Remitting MS progress to Secondary-Progressive MS, in which the symptoms of MS may wax and wane, but the disease progresses overall. In contrast, Primary-Progressive MS patients experience a slow but continuous worsening of MS symptoms without periods of remission. The final type of MS, Progressive-Relapsing, is noted by immediate disease progression with occasional periods of remission.

The current market basket of drugs used to treat MS consists of Copaxone® and Novantrone® as well as the beta-interferons. In 1993, Betaseron® was the first beta-interferon approved, followed in 1996 by Avonex® and in 2002 by Rebif®. All of the beta-interferons are indicated for the treatment of Relapsing-Remitting MS. Avonex® is administered as a once-weekly intramuscular injection, while Betaseron® is administered every other day and Rebif® three times per week. In 1997, Copaxone® was introduced to the market. Copaxone® is not an interferon but instead works by blocking nerve-damaging cells. Novantrone® has been on the market for many years as an anti-cancer drug, and in 2000 it received approval for MS. Due to its side effect profile and monitoring requirements, it is typically reserved for more severe cases.

Pipeline: Perhaps the most promising compound in the pipeline for MS is Antegren™ (natalizumab). Antegren® is the first monoclonal antibody being developed for MS; it provides a different mechanism of action than currently available therapies. Because of its unique mechanism of action, Antegren® can be used for patients who have not responded to other MS therapies, and it can be used in combination with a currently available treatment. An oral version of Copaxone® is under development, but initial studies did not show a treatment benefit. Other drugs in development focus on the immune system and the source of inflammation, but they will not reach the market for a few years.

Interleukins

Primary Uses: Selected Cancers and Low Platelets in Cancer Patients

Interleukins are a group of proteins that play an important role in regulating some of the body's activities. Found within body cells, interleukins and other similar proteins are part of a family of chemicals called cytokines, which function as one of the body's messenger services. Cytokines carry important information between cells, instructing the cells to perform a certain function. For example, one cytokine may tell the body to increase the amount of cancer cells in a tumor, while another may be designed to decrease the number of platelets being manufactured by the body.

At least 27 different forms of interleukin have been identified in the body. They are named by number (interleukin-1, interleukin-2, etc.) and often abbreviated as IL-1, IL-2, and so on.

Drug therapy using interleukins is achieved either by increasing the amount of interleukins circulating in the body or by blocking their effects. The first interleukin product, Proleukin® (IL-2) was approved by the FDA in 1992 for the treatment of kidney cancer. Proleukin® works by assisting the body's own interleukins in attacking and killing cancer cells. It is typically administered in a hospital setting because of potential side effects. The second interleukin, Neumega® (IL-11) is approved for patients with low platelet counts following chemotherapy. Neumega® directly stimulates the development of platelets. It can be self-injected once daily until platelet levels return to normal, a process that usually takes 21 days or less. The third interleukin drug approved by the FDA does not enhance interleukin activity but instead prevents it. Kineret™ blocks the effects of interleukin-1, which is one of the prime causes of inflammation in rheumatoid arthritis patients. It is given as a self-injection on a daily basis. Therapy with Kineret™, unlike Proleukin® and Neumega®, is chronic in nature.

Pipeline: Significant research is taking place in the field of interleukins. Because there are so many potential sites of action (27 or more), identifying potential drug targets is important. Currently, at least 11 interleukin subtypes are under study for potential drug targeting. Diseases potentially treatable with these products include asthma, Crohn's disease, MS, lupus, psoriasis, dermatitis and many different forms of cancer. Despite this significant activity, no new interleukin drugs are expected on the market in the immediate future. Prestara™, a hormone-based drug with interleukin activity (but not a true interleukin), is a future candidate for approval.

Alfa-interferons

Primary Use: Hepatitis C

Like interleukins, interferons are natural proteins produced by the human body. They assist the body's other defenses in fighting off invading cells that can carry disease. Although interferons were discovered in the 1950s, the first was not approved for use until 1986. Because of their relatively non-specific effects, interferons are used in a wide variety of disease states. Three different forms of interferon are on the market today, and while they are all interferon molecules, they differ in their specific mechanisms of action and response to disease. Alfa-interferons, the first interferons introduced, are used for different types of cancer, hepatitis and genital warts. In 1993, the first beta-interferon was approved for the treatment of MS. A gamma-interferon, Actimmune®, was approved in 1990 for the treatment of a rare immune deficiency called chronic granulomatous disease. The remainder of this section will focus on alfa-interferon therapies.

The current alfa-interferon market consists of several products, although two newer products are receiving the most attention. The first alfa-interferons, Intron® A and Roferon®-A, were approved in 1986 for treating patients with hairy cell leukemia, a form of cancer. In subsequent years these products received additional indications for the treatment of hepatitis C and Kaposi's sarcoma, a cancer fairly common among AIDS patients. Intron® A and Roferon®-A are similar products, and both are produced using recombinant DNA technology. In 1989, the interferon Alferon N® was approved for the treatment of genital warts. Alferon N® differs from Intron® A and Roferon®-A in

that it is produced using human white blood cells rather than by recombinant DNA technology. A fourth alfa-interferon, Infergen®, was approved in 1997 for the treatment of hepatitis C. Infergen® differs from the aforementioned products in its chemical structure, so it is not a true alfa-interferon but it is very similar.

While interferons were used modestly with some success in different patient groups, their use grew dramatically with the approval of Rebetron™ in 1998. Rebetron™ combines Intron® A with the oral antiviral drug ribavirin for the treatment of hepatitis C. It was an immediate success due to the improved response rates seen with this combination therapy. The hepatitis C market surged in the following years as more patients were diagnosed and started on therapy. In 2001, a new form of Intron® A was introduced. Called PEG-Intron®, it offers similar effectiveness to Intron® but fewer injections per week (one versus three). PEG-Intron® was joined by a competing product, Pegasys®, in 2002. Pegasys® is also administered once weekly.

Pipeline: The interferon pipeline largely focuses on expanding the uses of existing drugs rather than developing new drugs. For example, alfa-interferons are being studied for the treatment of several cancers, including melanoma, non-Hodgkin's lymphoma and chronic myelogenous leukemia (CML). Research with gamma-interferon focuses on cystic fibrosis, asthma and ovarian cancer. A new class of interferons, the omega-interferons, is in early stages of development for hepatitis C and cirrhosis. One specific omega-interferon is being designed to target the liver, which may lessen the side effects seen with other interferons. Perhaps the most unique drugs in development are interferon antagonists. These anti-interferon drugs are expected to be tested for diseases, such as Crohn's disease and psoriasis, in which the overexpression of interferons is detrimental.

Heparins

Primary Use: Prevention of Blood Clots

Heparin products are also known as anticoagulants. Their primary role is the prevention and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT occurs in the deep veins of the body, most often in the veins of the legs. It can be caused by a variety of conditions, such as inactivity, obesity or trauma. Each of these conditions includes periods of decreased venous blood flow. When this occurs, the body starts to initiate its coagulation process, which ultimately leads to the formation of a blood clot. Most often a blood clot stays in the location where it is formed, such as the leg, resulting in localized pain and discomfort. However, sometimes a blood clot breaks loose from its location and enters the general circulation. If the clot reaches the arteries of the lung, it may result in a PE, which can be fatal.

Heparin is the standard of care for acute treatment of DVT and PE. The effects of heparin have been known for almost a century. Heparin binds to a specific mediator in the coagulation process and works quickly to dissolve blood clots. It is usually given by intravenous infusion in a hospital setting. Heparin is also widely used for the prevention of DVT, as a subcutaneous injection. However, heparin therapy requires intense monitoring, so opportunities for patients to self-inject heparin remained limited until the 1990s, when heparin therapy was enhanced by the approval of Lovenox®, the first low-molecular-weight heparin. Lovenox® and subsequent similar products

contain a smaller piece of the heparin molecule, and they are administered as self-injections. Low-molecular-weight heparins are equally as effective as heparin for the treatment of DVT and PE, and they provide a safety benefit over regular heparin because typically monitoring is not required. Two products, Lovenox® and Innohep®, are approved for the prevention and treatment of DVT, while two additional products, Fragmin® and Arixtra®, are approved for the prevention of DVT. Technically, Arixtra® is not a heparin, but it works similarly to the low-molecular-weight heparin products.

Pipeline: Currently, research focuses on oral products that could eventually replace the injections now required for the treatment of DVT. Warfarin is a widely available oral anticoagulant, but it takes a few days to work, which is why heparin and warfarin are given together to many patients who have experienced DVT. The product closest to market is Exanta™, which is a direct thrombin inhibitor being studied for both prevention and treatment of DVT. Other products in the pipeline are designed to target specific factors that cause coagulation, and several companies are designing oral versions of heparin itself.

LHRH Analogs

Primary Uses: Endometriosis and Prostate Cancer

LHRH is an abbreviation for luteinizing hormone-releasing hormone, and an LHRH analog is a drug that mimics the effect of LHRH in the body. Given on a short-term basis, LHRH increases the levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are the hormones responsible for increasing the levels of testosterone (in males) and estrogen (in females). As a result, LHRH analogs are often used as part of an infertility regimen in women. However, if LHRH is given on a more chronic basis, levels of FSH and LH are reduced, resulting in low levels of testosterone or estrogen. Conditions in which low levels of FSH and LH are desirable include prostate cancer, endometriosis and central precocious puberty. Because LHRH analogs decrease the levels of sex hormones in the body, they have the effects of chemical castration in males and cessation of menstruation in females. These effects are reversible upon discontinuation of therapy.

The most commonly used LHRH analog is Lupron®. Lupron® comes in many different formulations, including a subcutaneous injection and several long-acting, or depot, formulations that can be given in intervals of up to 4 months. An implanted version, called Viadur®, is active for one year. A second LHRH analog, Zoladex®, is also available as a subcutaneous injection in 1-month or 3-month depot formulations. Zoladex® is commonly given with oral chemotherapy drugs as part of a prostate cancer regimen.

Pipeline: Significant new drug development does not appear to be taking place in the area of LHRH analogs. The primary focus will continue to be designing delivery systems that are effective and long-acting, thereby decreasing the number of injections needed over a period of time.

Tumor Necrosis Factor Inhibitors

Primary Uses: Rheumatoid Arthritis, Crohn's Disease and Psoriasis

Part of the body's immune system, tumor necrosis factor (TNF) is a protein that helps stimulate the body's response to infection or disease. It gets its name because one of its first known activities was the breakdown of certain cancer cells. Since its initial discovery, TNF has been implicated as a cause of cachexia, which is the loss of lean body mass in patients with cancer, and as an inflammatory mediator in diseases such as rheumatoid arthritis (RA), Crohn's disease and psoriasis. Joint destruction can also occur when TNF levels are high. Drug therapy is designed to target circulating TNF and block its effects.

Three TNF-inhibitors are currently on the market. They differ in chemical composition, approved uses and methods of administration. The first anti-TNF drug was Remicade®, approved by the FDA in August 1998 for the treatment of Crohn's disease. Since its initial approval, Remicade® has received approval for use in RA. It is given in a physician's office by intravenous infusion every 4 to 8 weeks depending on the severity of the disease. The FDA approved the second TNF-inhibitor, Enbrel®, in November 1998. First approved for use in RA, Enbrel® has since added additional indications for juvenile RA and psoriatic arthritis, which is arthritis caused by the skin disease psoriasis. It is self-administered twice weekly by subcutaneous injection. Remicade® and Enbrel® received additional competition at the end of 2002 when the FDA approved Humira™ for the treatment of RA. Like Enbrel®, Humira™ is a self-administered subcutaneous injection. However, Humira™ is given less frequently than Enbrel®, with an every-other-week dosage regimen.

Pipeline: The pipeline for TNF-inhibitors is quite large, in both the number of products and the number of new uses for existing products. Each of the currently marketed TNF-inhibitors is being studied for effectiveness in psoriasis, a disease with few effective treatment options. Remicade® is being studied for asthma to see if the anti-inflammatory effects seen in RA and Crohn's disease can be applied to a respiratory disease. Efforts are also under way to simplify dosage regimens. Once-weekly injections are being studied for Enbrel®. A subcutaneous version of Remicade® that is in development would allow self-injections. On the new drug front, the closest product to market is likely CDP-870, which offers monthly subcutaneous dosing. Other unique drugs in development include onercept, a TNF-binding protein; and DPC 333, an oral therapy to inhibit an enzyme that produces TNF.

Colony Stimulating Factors

Primary Use: Increasing White Blood Cells in Cancer Patients

White blood cells called neutrophils are the body's primary defense against infections. A low number of neutrophils in the body is called neutropenia. Neutropenia is a serious condition, because even the smallest infection can cause serious complications or even death. The condition occurs most often in people receiving chemotherapy for cancer and in bone marrow transplant recipients. Cancer chemotherapy drugs are so strong and toxic that they often destroy healthy cells in addition to the cancerous cells. During the time that the body takes to regenerate healthy white cells, patients are at the greatest risk of infection. Many years ago the only course of action was trying to prevent infections by administering multiple antibiotics while waiting for the body to regenerate new white blood cells from the bone marrow. In recent years, new therapies that

directly stimulate the bone marrow into producing more white blood cells were developed. These therapies, called colony stimulating factors, reduce the risk of serious infections, allowing patients to stay on their scheduled cancer chemotherapy regimens.

Three colony stimulating factors are currently on the market. The first two, Neupogen® and Leukine®, were approved in 1991, and the third, Neulasta™, in 2002. Neupogen® and Neulasta™ contain the same active drug but differ in their methods of administration. Neupogen® is given on a daily basis, either subcutaneously or intravenously, until the patient's white blood cell count is at an acceptable level, which can be up to 2 weeks for chemotherapy patients and even longer for bone marrow transplant patients. A long-acting form of Neupogen®, Neulasta™ is given by subcutaneous injection at the start of each chemotherapy cycle. Leukine® is a slightly different form of colony stimulating factor used for specific types of cancer and in bone marrow transplantation. It is given primarily as an intravenous infusion, but it can also be given subcutaneously.

Pipeline: Because neutrophils are the body's natural defense against infection and because some current therapies specifically target neutrophils, opportunity for new drug development is limited. It is possible that new therapies could further enhance the delivery of drugs to the body or perhaps complement existing therapies, but no such therapies are in advanced clinical trials.

Erythroid Stimulants

Primary Use: Increasing Red Blood Cells in Patients with Kidney Disease or Cancer

The body manufactures two different types of blood cells: white blood cells, some of which are described above, and red blood cells (erythrocytes), which have the primary purpose of carrying oxygen from the lungs to the rest of the body. Red blood cells are generated in the bone marrow, and their production is stimulated by a protein called erythropoietin. When the circulating amount of red blood cells is decreased, anemia results. Conditions that can cause anemia include kidney disease and chemotherapy for certain kinds of cancer. If the body's own bone marrow cannot generate enough new red blood cells to replace those lost by disease or drugs, a blood transfusion is usually necessary. Research done in the 1980s led to the development of an erythroid stimulant — recombinant erythropoietin — which is used to supplement the body's own erythropoietin and limit the occurrence of anemia and the resulting need for blood transfusions.

The current recombinant erythropoietin market consists of three products, two of which are the same molecule. The first product, Epogen®, was approved in 1989 for use in patients with advanced kidney disease, including dialysis patients. The company that discovered and developed Epogen® then licensed certain rights of the product to another company, and the drug was brought to market in 1990 as Procrit®, which is used for anemia related to cancer chemotherapy. Even though the two different products, Epogen® and Procrit®, are being marketed for different diseases, the active ingredient, erythropoietin, is the same in both products. In 2001, a next-generation erythropoietin product, Aranesp™, was brought to market for anemia caused by either kidney disease or chemotherapy. Aranesp™ is a slightly modified version of erythropoietin that is approved for less frequent dosing than Epogen® and Procrit®.

Pipeline: Opportunities for new drugs to compete in the class of erythroid stimulants may prove difficult, as existing therapies provide supplemental erythropoietin to the body's own stores of the protein. However, research is being done on compounds that enhance the delivery of erythropoietin to the cells that need it. One such method of enhancing delivery is through gene activation. Currently, supplemental erythropoietin is produced by inserting the gene for human erythropoietin into the cell of an animal, where it is grown for mass production. Gene activation takes place within the human cell by "turning on" the gene to produce more erythropoietin. Another method of erythropoietin delivery, in very early stages of development, uses inactive erythropoietin that is injected, stored in the body and then activated by an oral drug.

Growth Hormone

Primary Use: Growth Hormone Deficiency

Growth hormone is secreted by the pituitary gland. When it reaches the liver it stimulates the production of another hormone, called insulin-like growth factor one (IGF-1), which is responsible for the effects typically associated with growth hormone. Growth hormone deficiency occurs when the production of growth hormone is disrupted. Initially, growth hormone was obtained from human cadavers. That practice was stopped in the 1980s, when therapy was shifted to recombinant versions of human growth hormone. Therapy with growth hormone can be divided into three categories: patients with documented growth hormone deficiency, patients with short stature due to a concomitant disease and patients with muscle wasting due to AIDS.

The first recombinant growth hormone, Protropin®, was approved in 1985 for use in children with growth failure. Protropin® was soon followed by several products (Humatrope®, Nutropin®, Genotropin®, Norditropin® and Saizen®). All of these products are approved for use in children with growth hormone deficiency and some are also approved for use in adults. An additional growth hormone product, Serostim®, was approved by the FDA in 1996 for the treatment of AIDS wasting, a disorder in which the body uses lean muscle mass instead of stored body fat for energy. All growth hormone products can be self-administered as subcutaneous injections, and most are given on a daily or almost-daily basis. Nutropin® is also available as a long-acting depot formulation, which reduces the number of injections to one or two per month.

Pipeline: The development of new drugs to treat growth hormone deficiency focuses on alternative delivery systems. At least two oral versions of growth hormone are being developed, as is a nasal version, although each is a number of years from the market. A fourth product contains growth hormone attached to the protein albumin. This design may allow for less frequent dosing.

Intravenous Immune Globulin (IVIG)

Primary Use: Immunodeficiency Caused by Genetics, Cancer or HIV

IVIG products are used for immunodeficiencies, conditions in which the body's immune system is not working properly. The immune system is the body's defense against infection, and it consists of many different types of cells and proteins. When these cells and proteins fail to work properly, the body is more susceptible to infections. The most common immunodeficiency is caused by a genetic defect that is usually passed from parents to children. Immunodeficiencies present at birth are called primary immunodeficiencies. More than 70 different forms of primary immunodeficiencies, with varying levels of severity and incidence, have been identified to date.

IVIG is a therapy for patients with immunodeficiencies caused by a lack of antibodies. Antibodies are large proteins, also known as immunoglobulins, which attach to foreign substances, such as bacteria, and "hold" them until another immune cell, the macrophage, destroys them. Without enough circulating antibodies, persons with an immunodeficiency are more susceptible to even the mildest infections. Something as simple as a cold can be very serious to a person with an immunodeficiency. IVIG is given to these patients to provide a higher level of circulating antibodies that work to prevent future infections. IVIG is made from human blood that has been purified to prevent contamination. Typically, it is administered by intravenous infusion, either at home or at a medical clinic. Therapy with IVIG is repeated every 3 to 4 weeks for the patient's lifetime. IVIG products include Gammagard®, Venoglobulin®-S, WinRho SDF® and Gamimune® N. Each of these products is a unique formulation; not all have the same FDA-approved uses.

Pipeline: Current research in the area of immunodeficiencies focuses on both drug and non-drug therapies. Gene therapy is the most active area of research. Because a primary immunodeficiency is the result of a genetic defect, research is being done to see if inserting healthy genes into the cells of an immunodeficient patient results in the production of healthy cells. Early results are encouraging, but widespread treatment with gene therapy is years away. Other genetic research is being conducted using stem cells, which are cells taken from umbilical cord blood. When pregnancy screening indicates that a primary immunodeficiency is probable, umbilical cord blood is collected during delivery, the stem cells are taken out and modified genetically, then they are transfused into the child. This technique is also years away from widespread use.

Clotting Factors

Primary Use: Hemophilia

Typically seen in males, hemophilia is an inherited bleeding disorder caused by a shortage of blood-clotting factors. A person with hemophilia has an excessive risk of bleeding. The two different types of hemophilia are called A and B. Hemophilia A, also called classic hemophilia, is the most common, and it is caused by a deficiency in clotting factor VIII. Hemophilia B is caused by a deficiency in clotting factor IX. An additional bleeding disorder, von Willebrand's disease, is related to the function of platelets, cells that assist with blood clotting.

The treatment of hemophilia requires administration of clotting factors. Historically this was accomplished by blood transfusions, but the amount of clotting factors in a typical transfusion was not enough to treat the bleeding disorder sufficiently. In the 1960s, a concentrated form of factor VIII, also known as cryoprecipitate, was discovered. Administration of cryoprecipitate did not require a blood transfusion, which was beneficial to patients. A few years later, the introduction of freeze-dried forms of factor VIII and factor IX, derived from human blood plasma, allowed hemophilia patients to administer clotting factors at home. Unfortunately, some of these earlier products were contaminated with viruses, so even though hemophilia patients were able to control their bleeding disorder, a few patients were infected with diseases such as HIV or hepatitis. More recent products are recombinant in nature or are highly purified, so the risk of infection essentially has been eliminated. Recombinant factor VIII products include Kogenate® FS, Recombinate™ and ReFacto®, while plasma-derived products include Alphanate®, Humate-P®, Hemofil® M, Monarc-M™ and Monoclate-P®. For factor IX, the only recombinant product is BeneFix®, and common plasma-derived products include AlphaNine® SD and Mononine®. The dosing of clotting factors is highly variable since it is based on patient weight as well as on the severity of disease. All clotting factors are given intravenously, and most patients self-infuse at home.

Pipeline: As with several other diseases, the most intriguing research in the field of hemophilia is gene therapy. The gene that causes hemophilia is known, and if this gene were to be modified to become a "normal" gene, hemophilia might be cured. Several gene-therapy products are in clinical trials, including both factor VIII and factor IX products. It will likely be a number of years before these products make it to market. Closer to market are recombinant products that are free of any forms of albumin, which has been linked to impurities (and resulting infections) in the past.

Actions to Mitigate Impact of Cost Trend

The annual growth in PMPY ingredient costs continued to rise in 2002, reaching an all-time high of 18.5 percent. Inflation and utilization rate increases were substantial, 7.5 percent and 6.3 percent, respectively. Over the next 5 years, Express Scripts anticipates that PMPY prescription drug costs will continue to increase at still substantial but somewhat lower annual rates of growth as more generic products are prescribed when brand products lose patent protection.

Employers, health plans and other plan sponsors confront numerous challenges as they strive to continue providing an affordable drug benefit to their employees and members in this environment of rising pharmacy costs. The various approaches plan sponsors can adopt in dealing with the challenges of rising drug costs are presented in the remainder of this section.

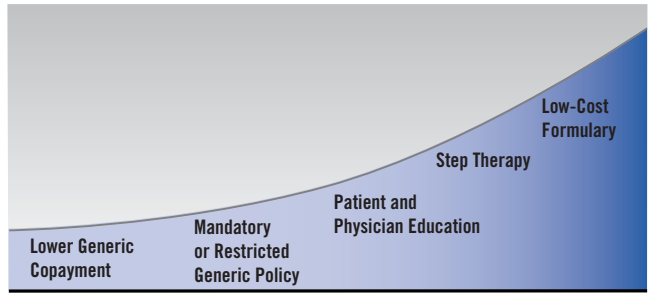
Take Advantage of Generics

As noted in the introduction, a number of significant brands recently have lost or soon will lose patent protection. In turn, the cost-saving potential for the plan sponsor and member can be substantial. However, generic availability does not automatically translate into cost savings. Delays in patent expiration, the introduction of new strengths and dosage forms, the lack of generic product marketing relative to brands, and the development of new brand products can limit the cost-saving potential of generics.

As illustrated in last year's *Drug Trend Report,* the typical life cycle of a prescription chemical entity may mitigate the potential that generic product availability can have as a cost-management strategy. Market share begins to decline prior to generic availability. The market share erosion of these brand-name, soon-to-be generic products varies, depending on whether strong competition exists within the class and/or whether a new, innovative brand product is waiting to capture market share. Even after the generic becomes available, the market share of that chemical entity (now the brand and generic versions combined) continues to decline for two reasons. First, generic drug manufacturers are essentially in competition with themselves. One manufacturer may make the same product for several other companies to distribute, or several manufacturers could be producing and distributing the same generic product. Consequently, it is not in the interest of generic manufacturers to spend money to advertise their specific generic product, because the benefit will be shared by competing generics. Second, the economics of the generic industry leave it with far fewer dollars for product promotion than brand-name competitors. Market share typically levels off at a point significantly below the brand drug's peak market share level.

To optimize the cost-savings potential of generics, plan sponsors should counteract such tactics by effectively promoting the appropriate use of generics. Programs that promote generics can be depicted on a continuum of intensity as is shown in Figure 11. Each of these programs is reviewed on the following pages.

Figure 11
Continuum of Approaches to Maximizing Generic Opportunities



Lower Generic Copayment: One of the most important strategies for promoting generic use is to keep the generic copayment low — $5 to $7.50. Lower copayments provide members with a financial incentive to use generics rather than brands. In addition, based on Express Scripts' research, the brand copayment should be at least $8 to $10 higher than the generic copayment for members to have adequate incentive to use generics when appropriate. Plan sponsors that have increased generic copayments to $10 or more in recent years may want to consider decreasing the generic copayment and, correspondingly, increasing the brand copayment. Although consumers are somewhat insensitive to prescription copayment changes, offering them a substantially lower generic copayment will lead to increased generic use. Also, at a $10 copayment for generics, plan sponsors will be asking members to pay more than 50 percent of the cost of many generics.

Mandatory or Restrictive Generic Policy: A generic policy represents a sound way to optimize the use of generics. Under a mandatory generic program, the member pays the generic copayment plus the cost differential between the multi-source brand and its generic equivalent, regardless of whether the physician allows generic substitution. In a restrictive generic program, the member pays the generic copayment plus the difference between the cost of the multi-source brand and its generic only if the member insists on having the multi-source brand, despite the physician allowing generic substitution. Express Scripts' research indicates that a generic policy provides additional savings even if a plan already has a lower copayment for generics than for brands (i.e., a two-tier or three-tier copayment). As reported in the 2001 *Drug Trend Report,* about two-thirds of the consumers who were surveyed said that generics are as good as brands, suggesting that generics are acceptable to a substantial majority of consumers. More importantly, the minority of consumers who disagreed thereby indicated their willingness to pay more for the brand medication. Accordingly, a generic policy represents a sound benefit design approach. Indeed, three-fourths of Express Scripts clients have either a mandatory or restrictive generic policy.

Patient and Physician Education: Efforts to encourage greater use of generics may be limited by physicians' unwillingness to prescribe them, as well as by consumers' reluctance to use them. While consumers are generally supportive of generics, a key challenge is that members often are not aware that a generic alternative is available, particularly when the generic is a different chemical entity — a therapeutic alternative — from the medication prescribed. This lack of awareness may seem surprising given the continued growth in consumerism. However, brand-name advertising messages, coupled with a lack of generic awareness among physicians, both contribute to a lack of generic awareness among consumers.

On the flip side, 85 percent of respondents to a February 2002 national survey conducted by Knowledge Networks for Express Scripts said they wanted information on ways to save money on prescription drugs. This percentage grows to 91 percent for respondents aged 55 to 64. When these higher utilization groups understand and respond to savings opportunities, the positive financial effect is even greater.

When addressing topics such as personal health and prescription drugs, messages from well-known sources have the greatest effectiveness. To get the most value from member education, PBMs and plan sponsors should collaborate so that members recognize the source of the information. Survey participants indicated that co-branded materials sent from familiar sources are more likely to gain their attention.

Patient education about generic medications can take many forms. Express Scripts offers an Internet tool that lets members view their out-of-pocket cost for a drug, as well as the cost of an available generic alternative when a brand-name drug is requested. This PriceCheck™ feature lets members see what they will pay for their prescriptions before having them filled at the pharmacy. It gives members the information needed to make cost-effective choices about their medication alternatives — choices that provide savings for both the member and the plan sponsor. Express Scripts' research shows the power of providing the right kind of information at the time the consumer is making a decision. Approximately 50 percent of members who had a mail benefit and who used PriceCheck™ to price maintenance medications began using mail service for these prescriptions.

For plan sponsors with a concentration of members in a given geographic region, physician outreach should be considered as part of a patient and physician education strategy to promote generics. Research has shown that physicians are not always receptive to prescribing generics. However, academic detailing with physicians can be effective at altering fundamental prescribing patterns. These programs are successful because they provide physician-specific prescribing profiles, use a clinician to discuss the merits of generics and provide rigorous clinical evidence that supports the appropriateness of the generic.

Beyond academic detailing, the next evolution in promoting optimal physician prescribing is RxHub, an independent venture formed by Express Scripts, AdvancePCS and Medco Health Solutions to advance the efficiency and safety of the prescription writing process. RxHub will address the information gap that exists among physicians, pharmacies, health plans and PBMs. The system created by RxHub allows physicians who use electronic prescribing devices

to connect directly to PBMs, access patient-specific coverage information (including the appropriate formulary) and receive real-time notification of potential drug interactions and side effects. The resulting prescription can be sent electronically to the patient's preferred pharmacy for fulfillment. Through RxHub technology, prescription use can become more cost-effective and safer.

Step Therapy: A step therapy program requires the member to try a less expensive drug, such as a generic, for a specified period of time before the plan sponsor will pay for the originally prescribed medication. The unprecedented availability of generics provides a wealth of clinically and financially appropriate step therapy opportunities. In addition to the immediate savings achieved, step therapy represents a longer-term strategy for encouraging generic use, because physicians' prescribing habits may change.

Low-Cost Formulary: The most aggressive strategy a plan sponsor can adopt to promote the use of generics is to implement a low-cost formulary — a closed formulary consisting primarily of generic products. As more branded products lose patents, it is possible to increase the use of generics through formulary design. The only branded products covered in the low-cost formulary are in therapy classes without a clinically equivalent generic. A low-cost formulary focused on generics will provide substantial savings to a plan sponsor because it represents the most effective strategy to promote generics.

Designing the Prescription Benefit Plan

Although the promotion of generics is a critical cost-management approach, an overall cost-management strategy must be more comprehensive. Four key steps are involved in designing an overall cost-management strategy.

Step 1: Formulary Development

Formularies, which are lists of covered or preferred drugs, are the backbone of pharmacy benefit design. Through an independent Pharmacy and Therapeutics Committee, Express Scripts offers a range of formularies to meet the varying needs of plan sponsors. In formulary development, a drug's clinical benefit, AWP, potential member and physician disruption and upcoming market dynamics (e.g., new generics) are all considered.

Step 2: Cost-Sharing Structure

After establishing a formulary, one of the first questions a plan sponsor addresses is whether to institute copayments or coinsurance. Express Scripts' research shows similar drug use patterns among co-insurance and copayment plans. The only evident advantage of co-insurance is that cost-sharing automatically keeps up with drug cost increases, while copayment designs require copayment increases every few years. However, because of the unpredictability of out-of-pocket costs for members, about 13 percent of Express Scripts members with an integrated benefit have co-insurance. When selecting a copayment structure, a plan sponsor can institute one, two, three or more levels. Nearly 55 percent of members with an integrated retail and mail benefit are enrolled in a three-tier copayment plan in which the lowest copayment is for generics and the highest for non-formulary brands, with the middle tier reserved for formulary brands.

Three-tier copayments respond to growing consumerism by allowing members to save money through choosing the less expensive therapeutic alternative. In a study published in *Medical Care,*[33] Express Scripts found that the three-tier structure resulted in significant savings for plan sponsors while having no effect on emergency room use, inpatient hospital visits or physician office visits. Some plan sponsors, seeking even more trend management, are instituting a closed formulary that only covers generic and formulary brand medications. An Express Scripts' study found a substantial savings in drug expenditures for a plan that implemented a closed formulary relative to a matched comparison sample with an open formulary.[34]

Step 3: Copayment Amount

Regardless of whether a plan sponsor opts for a two- or three-tier copayment plan, it is important that the level of copayments be set appropriately. To align plan sponsor and member incentives, Express Scripts recommends cost-sharing targets by tier of about 20 percent for generics, 20 percent for formulary brand-name drugs and 40 percent for non-formulary brand-name drugs. In 2002, the typical three-tier plan for Express Scripts clients was under $10 for generics, almost $20 for formulary brand drugs and over $35 for non-formulary brand drugs.

Step 4: Point-of-Service (POS) Programs That Reinforce Benefit

Formulary and cost-sharing choices can be reinforced real-time through the POS system. Plan sponsors can easily implement benefit exclusions, quantity limits, step therapy, and mandatory and restrictive generic programs at the time the claim is submitted for adjudication. Prior authorization (PA) programs require a patient to meet certain age requirements or have a documented diagnosis to receive a prescription of a given medication. A recent unpublished Express Scripts' study found that PA provides significant plan sponsor savings.

Before deciding to implement plan design changes, many plan sponsors factor into their decision-making process the potential impact such changes could have on member satisfaction. For example, whenever a plan sponsor changes the copayment amount, the potential member impact is an important consideration. An unpublished Express Scripts' study found that copayment changes produced a temporary increase in call center volume, which returned relatively quickly to call levels prior to the change. For every additional call related to a plan design change, the plan sponsors studied saved between $116 and $698.

Injecting an element of member choice can be central to mitigating the negative effect of plan changes on member satisfaction. Member choice is an underlying characteristic in tiered copayment systems. In a two-tier copayment system, the member has the choice between paying a less expensive generic copayment or a higher brand copayment, assuming that the drugs are therapeutically equivalent. In a three-tier copayment system, the member potentially has even more choice — an inexpensive generic copayment, a higher formulary brand copayment and an even higher non-formulary brand copayment.

33 Motheral BR, Fairman KA. Effect of a three-tier prescription copay on pharmaceutical and other drug utilization. *Medical Care.* 2001;39(12):1293-1304.

34 Motheral BR, Henderson RR. The effect of closed formularies on prescription drug use and costs. *Inquiry.* 1999-2000 Winter;36(4):481-491.

Express Scripts also helps plan sponsors enhance member satisfaction through a pharmacy benefit strategy called Express Choice™, which enables sponsors to offer multiple pharmacy plans from which members can choose. This approach responds to consumer choice and at the same time ties pharmacy use more directly to member financial responsibility. For example, an employer could provide one package for all drugs, regardless of the type of condition the drug treats, and another package that excludes coverage of drugs that have less expensive alternatives and of drugs used for cosmetic purposes. The employee selecting the richer benefit pays the incremental costs attached to the coverage of additional drugs. In addition to drug coverage, plan options can vary in the size of the retail pharmacy network and in the number and magnitude of copayments, as well as in other features such as the inclusion of a mandatory generic program. A member choice plan provides the employee open access to all drugs, but places part of the financial burden on the employee for his or her choices. One important consideration when adopting this strategy is whether to maintain some element of insurance in the pricing decision. A key assumption in insurance is that the price of the benefit should be spread across both the healthy and sick or, put another way, between low- and high-utilizers. This principle entails low-utilizers subsidizing the costs of high-utilizers. Calibrating the expected distribution of high- and low-utilizers across the various options for underwriting purposes is very difficult.

The specter of rising prescription drug costs will remain with us for the foreseeable future. As is evident from the discussion in this Report, there are a number of approaches that plan sponsors can take to manage these drug cost increases. Express Scripts works closely with clients to develop the specific approaches that best meet the needs of each client.