

Projecting future drug expenditures—2006

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Total prescription drug expenditures in the United States increased by 8.7% from 2003 to 2004, with total spending rising from \$218.5 billion to \$237.6 billion.¹ This indicates a continued moderation in the growth of prescription drug expenditures, which increased by 18% between 2000 and 2001, by 12% between 2001 and 2002, and by 12.5% between 2002 and 2003. This growth was also slower than the 11.9% increase in prescription drug expenditures projected by the Centers for Medicare and Medicaid Services (CMS).² This slower growth has been attributed to a decrease in the growth of prescription drug prices.³ While the overall increase in prescription drug expenditures was slower than in previous years, it remained higher than the projected growth in total health care expenditures and the growth in expenditures for hospitals and physician services, keeping prescription drug costs at the forefront of national health policy debates.²

Various recent publications have also noted a decrease in the growth of

Purpose. Drug expenditure trends in 2004 and 2005, projected drug expenditures for 2006, and factors likely to influence drug costs are discussed.

Summary. Various factors are likely to affect drug costs, including drug prices, drugs in development, and generic drugs. In 2004 there was a continued moderation of the increase in drug expenditures. Drug expenditures increased by 8.7% from 2003 to 2004. Through the first nine months of 2005, expenditures increased by only 8.1% compared with 2004. This moderation can be attributed to several factors, including the continued trend toward higher prescription drug cost sharing for insured consumers, growing availability of generic drugs, and lack of "blockbuster" new drugs in recent years. Drug expenditures in 2006 will likely be influenced by similar factors, with few costly new products reaching the market, increased concern over product safety slowing the diffusion of those new agents that do reach the market, and sev-

eral important patent expirations, leading to slower growth in expenditures.

Conclusion. Forecasting and managing rising drug expenditures remains a challenge. Pharmacy managers must remain vigilant in monitoring drug costs in their health system and take a proactive role in pursuing efficient drug utilization. The dynamic health policy environment further complicates drug budgeting and must be considered, especially in integrated health systems responsible for managing inpatient, outpatient, and clinic drug costs. The comparison of health-system-specific data and trends with the national information presented in this article may provide a useful context when presenting institutional drug costs to senior management.

Index terms: Administration; Budgets; Control; Costs; Drug use; Drugs; Economics; Patents; Pharmacy, institutional, hospital; Prescriptions; Pricing; Product development; Rational therapy; Toxicity

Am J Health-Syst Pharm. 2006; 63:123-38

prescription drug expenditures. Strunk et al.⁴ reported a 7.2% growth for prescription drug expenditures in 2004 for an insured population (ex-

cluding specialty injectable drugs), which was estimated to account for 21% of the growth in total health care expenditures. Those authors re-

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Mr. Vermeulen is a member of speakers' bureaus and receives research funding from Pfizer and Amgen. Dr. Schumock has consulted for or received research funding from Abbott, TAP, Scios, Glaxo, and Pfizer. The ASHP Section of Pharmacy Practice Managers provided support for the development of this article. Douglas Scheckelhoff, M.S., and several anonymous reviewers are acknowledged for their contributions to this article.

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DOI 10.2146/ajhp050446

ported that overall health care expenditures increased by 8.2% in 2004 and that hospital outpatient care expenditures were the main driver of growth in health care expenditures in that year. Overall, inpatient and outpatient hospital expenditures accounted for 54% of the growth in expenditures. Heffler et al.³ have projected a deceleration in the growth of prescription drug expenditures to 9.7% in 2014. This trend may be attributed in part to an increasing cost-sharing burden on consumers. A recent survey showed that 68% of insured workers were enrolled in plans with three- or four-tiered drug benefit designs (requiring significant out-of-pocket copayments) in 2004, compared with only 27% in 2000.⁵ Furthermore, a decrease in prescription drug expenditures may result from the increasing enrollment in high-deductible health insurance plans.⁶ Almost half of employers surveyed expected to further increase their employees' responsibility for prescription drug costs in 2005, a trend likely to continue through 2006.

Hospital expenditures continue to be the single largest component of health care costs, accounting for 31% of national health care expenditures, despite continued decreases in inpatient length of stay.² Increases in outpatient service utilization slowed the rate of inpatient growth in the 1990s. Total hospital inpatient expenditures increased by 5.8% from 2003 to 2004 (based on nine months of data), which was higher than the 4.1% increase in hospital expenditures seen from 2002 to 2003.² Total inpatient expenditures per discharge increased by 5.0% to \$7987, and the number of hospital discharges increased by 0.7% through the first nine months of 2004. However, the cost of hospital care and labor appears to have stabilized after years of significant increases.⁴ Nonetheless, it is expected that real per capita spending on hospital services will increase by 55–75%

from 2002 to 2012.⁷ Technology growth, including the development of new pharmaceuticals, also contributes to increased expenditures, and it is expected that hospital drug expenditures will continue to grow and remain a cost-containment target.⁸

The fastest-growing area for overall prescription drug expenditures was biological agents, which grew by 17% from 2003 to 2004.¹ There was a 2.4% increase in the number of prescriptions filled during those years. Growth in the number of prescriptions filled continues to decelerate, after growing by 9% in 1999.⁹ IMS Health has projected that total drug expenditures will increase 7–10% in 2005.¹⁰

In our 2005 drug expenditures forecast, we predicted a growth rate of 6–9% for hospital drug expenditures, 12–15% for clinic-administered drug expenditures, and 10–12% for outpatient drug expenditures.¹¹ During the first nine months of 2005, the growth rate for hospital drug expenditures was 5.6%, which was similar to our projected rate of growth. Volume and drug mix accounted for 2% of the growth, new drugs accounted for 1%, and price inflation accounted for 2% of the growth in hospital drug expenditures in 2005. Drug expenditures for clinics increased by 11% through the first nine months of 2005 (compared with the same time period in 2004) after increasing by 22% from 2002 to 2003. This growth rate is lower than our projected growth of 12–15%. This lower growth rate for drug expenditures in clinics can largely be attributed to the –1% price inflation for these drugs. Most of the drugs administered in clinics are either oncology agents or biologicals. In developing the 2005 forecast for clinics, we expected some price inflation for these drugs. Thus, the negative price inflation explains much of the discrepancy in our forecast for drug expenditures in clinics. Drug expenditures for outpatient and ambulatory

care settings (including mail order) increased by only 4.9% in the first nine months of 2005.¹ This growth was substantially lower than our forecast for 2005 in this setting. Factors that contributed to the deceleration of outpatient prescription drug expenditure growth include significant patent expirations in 2002 and 2003 (e.g., omeprazole, fluoxetine, metformin, lisinopril), increasing competition among manufacturers of generic drugs, conversion from prescription to nonprescription status of commonly used drugs (e.g., non-sedating antihistamines, proton pump inhibitors), and reductions in the use of several products for which safety issues have emerged (e.g., hormone replacement therapy, cyclooxygenase type 2 [COX-2]-selective nonsteroidal antiinflammatory drugs [NSAIDs], selective serotonin-reuptake inhibitors [SSRIs] in children). Higher cost sharing by consumers remains an important factor in the smaller increase in outpatient drug expenditures in 2005.

This article projects drug expenditures by sector (outpatient, clinics, and hospitals) for calendar year 2006. It discusses factors related to drug utilization and drug costs, including drugs in development, the diffusion of approved drugs, and factors affecting generic drug availability. Other trends in health care likely to affect drug expenditures are briefly reviewed. The authors' intent is that this information will aid health care professionals in determining how future changes will affect drug-related expenditures in their practice. Some data in this article may not fully reflect events that have occurred after September 2005, when the article was finalized for publication.

Drugs in development

The drug pipeline can have considerable influence on prescription drug expenditures. To understand drug expenditure patterns, it is important to monitor and evaluate the

drug pipeline. In the past, we published a more detailed approach to monitoring and evaluating drugs in development.¹² In brief, while new drug approvals often translate into higher costs, in some instances (e.g., when “me-too” agents are approved) new market entries can be priced substantially lower than existing agents.¹³ Consequently, a new drug that replaces an existing agent may have a positive, negative, or neutral cost impact. Conversely, innovative therapies that treat diseases that were untreatable with existing medications universally translate into higher drug costs.

When considering the drug pipeline’s effect on prescription drug expenditures, it is important to consider broad indicators of the drug pipeline’s size, the time it takes for new drugs to reach the market, and the specific drugs that could be approved in 2006. Markers used to gauge the size of the drug pipeline include the number of new drugs approved by the Food and Drug Administration (FDA), the number of new drug applications (NDAs) filed with FDA, and the number of investigational new drug (IND) applications filed and active with FDA.

Number of approvals. In 2004, there was a considerable increase in the number of new drugs approved by FDA.¹⁴ A total of 36 novel medications (31 new molecular entities [NMEs] and 5 new biologics) were approved in 2004, an increase from the 21 and 17 new medications approved in 2003 and 2002, respectively.¹⁵ However, since the profile of agents approved in 2004 was atypical, the increase in approvals in 2004 has not translated into a widespread increase in drug costs.¹⁶ For example, 9 of the new approvals were orphan drugs, which, while having a substantial financial effect on some individual payors and provider organizations, have a limited effect on overall drug expenditures.¹⁷ Therefore, based on the number of truly new

drugs approved in 2004, it may appear that the late-stage drug pipeline is full, but the number of NDAs filed actually decreased from 110 in 2003 to 108 in 2004.¹⁸ While this difference may appear trivial, it is important to note that in 2003, the approval process for therapeutic biologics was transferred within FDA from the Center for Biologics Evaluation to the Center for Drug Evaluation and Research. Thus, the 2004 NDA number includes applications for biologics, which were not included in the NDA filing statistics for 2003.¹⁶

Despite the apparent slowdown in the late-stage drug pipeline, the early-stage drug pipeline has grown. The number of commercial IND applications filed with FDA, an indicator of the size of the early-stage drug pipeline, increased 39% from 2003 to 2004.¹⁹ When therapeutic biologics are included, 621 IND applications were filed in 2004.²⁰ IND application filings increased for anti-infective, urologic, medical imaging, and dermatological drugs, but decreased for cardiology and renal drugs.¹⁹ The total number of active INDs in 2004 grew at a more moderate pace of 6%. According to FDA, there were 4827 active commercial INDs in 2004, including INDs for therapeutic biologics.^{21,22}

Approval times. Approval times for drugs in development are expected to become longer during 2006. From 2003 to 2004, approval time remained relatively consistent. Median approval time for priority NMEs and biologics decreased from 6.7 months in 2003 to 6 months in 2004, but median approval time for standard NMEs and biologics increased slightly from 23.1 months in 2003 to 24.7 months in 2004.²³ Predicting the effect of changes in FDA leadership on the emergence of new pharmaceutical technologies is particularly important. For most of 2004 and the first half of 2005, FDA was led by Lester Crawford, and many senior positions were vacant during that

time.²⁴ After a five-month confirmation process, Crawford was finally confirmed to lead the agency in July 2005.^{22,25} Less than three months later, he resigned under heavy criticism for his handling of several medication safety issues, most notably the withdrawal of rofecoxib (Vioxx, Merck).²⁶ In the first lawsuit brought against Merck by plaintiffs claiming harm caused by rofecoxib, a \$253 million judgment was awarded. While the case is under appeal and the judgment will almost certainly be reduced, future lawsuits may cost Merck as much as \$55 billion.²⁷

Whether the approval process is slowed by a more cautious FDA or by manufacturers pursuing more exhaustive testing before applying for approval of new agents, the time required to bring a drug to market will almost certainly increase. There is already evidence of increased FDA approval times. In 2005, FDA issued more warnings for existing drugs and lengthened approval times for drugs in development. The agency has issued 11 public health advisories regarding drug risk, more than double the number issued in 2004, and 45 black-box warnings in the first half of 2005 versus 9 such warnings in this period in 2004.²⁸ Approval time in the first half of 2005 nearly doubled compared with the same time in 2004, and there is an indication that FDA will more often require multiple review cycles.²⁹

Expected approvals. Table 1 highlights selected drugs expected to be approved by FDA in 2006. Drugs with the potential to substantially affect drug expenditures include several new therapies for diabetes, including inhaled insulin, the cancer therapy panitumumab, and the anti-infective dalbavancin.

Panitumumab is an investigational product in a class of targeted cancer treatments called epidermal growth-factor-receptor (EGFr) inhibitors. It is the first fully human monoclonal antibody directed

against EGFr and is being evaluated as both a monotherapy and in combination with other agents for the treatment of various types of cancer, including colorectal, lung, and kidney.³⁰ Since panitumumab is fully humanized, it is a more attractive treatment than other EGFr therapies. The fully human nature of panitumumab may result in a decrease of infusion reactions, antigenicity, and allergic response. Approval of panitumumab could have a significant effect on clinic drug expenditures in 2006.

Approval of dalbavancin would significantly add to the anti-infective arsenal for the treatment of gram-positive infections. Dalbavancin is a unique, once-weekly i.v. lipoglycopeptide for the treatment of compli-

cated skin and soft-tissue infections caused by gram-positive bacteria, including the most difficult-to-treat strains of *Staphylococcus*, methicillin-resistant *Staphylococcus aureus* (MRSA).³¹ The once-weekly administration of this agent and its long half-life make it an attractive option for the treatment of MRSA infections.

If approved, the oral direct thrombin inhibitor ximelagatran (Exanta, AstraZeneca) has the potential to produce important clinical and economic changes in anticoagulation therapy. In 2004, FDA denied approval of ximelagatran because of hepatic toxicity concerns, but the manufacturer has continued to pursue development of the drug.³² Approval of ximelagatran does not appear to

be imminent. Even if approved in 2006, it would likely be approved only for short-term use (as it has in Europe).³³ Therefore, ximelagatran is not expected to have a significant impact on drug expenditures in 2006. However, even if the development of ximelagatran is abandoned and the drug is never marketed in the United States, other oral direct thrombin inhibitors remain under investigation. In the future, these agents will likely have a substantial effect on anticoagulation therapy and drug expenditures.

Diffusion of recently approved drugs

Diffusion is the rate at which innovations, such as new drugs, become widely used. The diffusion of

Table 1. Selected Drugs and Biologicals Expected To Be Approved by FDA between October 2005 and December 2006^a

Drug	Manufacturer	Indication(s)	Route	Expected Approval Date
Inhaled insulin (Exubera)	Pfizer/Nektar Therapeutics/Sanofi-Aventis	Diabetes	Inhaled	4th quarter 2005
Lenalidomide (Revlimid)	Celgene	Myelodysplastic syndrome	Oral	4th quarter 2005
Abatacept (Orencia)	Bristol-Myers Squibb	Rheumatoid arthritis	Injectable	1st quarter 2006
Alglucosidase alfa (Myozyme)	Genzyme	Pompe's disease	Injectable	1st quarter 2006
Dalbavancin	Pfizer	Gram-positive infections (including MRSA) ^a	Injectable	1st quarter 2006
Nebivolol	Mylan Laboratories	Hypertension	Oral	1st quarter 2006
Ranolazine (Ranexa)	CV Therapeutics	Angina	Oral	1st quarter 2006
Sorafenib (Nexavar)	Onyx/Bayer Pharmaceuticals	Advanced renal-cell carcinoma	Oral	1st quarter 2006
Alvimopan (Entereg)	Adolor/GlaxoSmithKline	Postoperative ileus	Oral	2nd quarter 2006
Anidulafungin	Pfizer	Fungal infections	Injectable	2nd quarter 2006
Decitabine (Dacogen)	MGI Pharma/Supergen	Myelodysplastic syndrome	Injectable	2nd quarter 2006
Rimonabant (Acomplia)	Sanofi-Aventis	Antismoking, antiobesity	Oral	2nd quarter 2006
Sitaxsentan (Thelin)	Encysive Pharmaceuticals	Pulmonary arterial hypertension	Oral	2nd quarter 2006
Sunitinib (Sutent)	Sugen/Pfizer	Advanced renal-cell carcinoma, gastrointestinal stromal tumor	Oral	2nd quarter 2006
Indiplon	Neurocrine Bioscience/Pfizer	Insomnia	Oral	2nd quarter 2006
Oblimersen (Gensense)	Genta	Leukemia	Injectable	3rd quarter 2006
Panitumumab	Abgenix/Amgen	Colorectal cancer	Injectable	3rd quarter 2006
Doripenem	Johnson & Johnson	Ventilator-associated pneumonia	Injectable	4th quarter 2006
Sipuleucel-T (Provenge)	Dendreon	Prostate cancer	Injectable	4th quarter 2006
Rufinamide	Eisai	Antiepileptic	Oral	4th quarter 2006
Vigabatrin (Sabril)	Ovation Pharmaceuticals	Anticonvulsant	Oral	4th quarter 2006
Vildagliptin	Novartis	Diabetes	Injectable	4th quarter 2006

^aSource: Medications in Development Database, University of Wisconsin Hospital and Clinics. MRSA = methicillin-resistant *Staphylococcus aureus*.

innovations that become widely accepted, including new drugs, follows a sigmoid-shaped curve.³⁴ For example, initial use of a new drug is often slow, but as familiarity with the drug grows, use increases rapidly until the drug is widely used and growth stabilizes. Therefore, in the first several years after a drug is available, it may not necessarily have an appreciable financial impact, but, as use of the drug grows, the drug becomes an important economic consideration. This pattern is particularly pronounced when new unlabeled indications emerge for recently approved drugs.

While this typical diffusion scenario continues for some recently approved drugs, a different diffusion trend has appeared over the past year. Safety concerns for several relatively new high-volume and high-cost drugs have resulted in the drugs' removal from the market or a clear decrease in their use. The dominant diffusion trend has shifted from rapid drug diffusion that fuels growth in drug expenditures to slower drug diffusion due to safety concerns, which moderates the growth in drug expenditures.

The most obvious example of this new diffusion prototype is the recent change in the use of COX-2-selective NSAIDs due to cardiovascular toxicity. The removal of the COX-2-selective NSAIDs rofecoxib and valdecoxib from the market and the FDA-mandated black-box warnings for celecoxib have reduced the thriving global market for COX-2-selective NSAIDs from \$6 billion in 2004 to an estimated \$2 billion in 2005.³⁵ In the United States, the mean number of prescriptions per month for these drugs decreased from approximately 4.5 million in 2003 to a mean of 1.4 million in the first six months of 2005.⁹ As described previously, the safety concerns surrounding these drugs will clearly affect the U.S. regulatory environment. It is also likely that these safety concerns will slow

the diffusion of many other new drugs. For example, the monoclonal antibody natalizumab (Tysabri, Biogen Idec/Elan) was approved in late 2004 for the treatment of multiple sclerosis, with promising data emerging on its use for Crohn's disease.^{17,36} In the last quarter of 2004 and first quarter of 2005, sales of natalizumab for nonfederal hospitals and clinics exceeded \$11 million.¹ However, after approximately three months on the market, the sale of natalizumab was suspended after three reports of drug-related progressive multifocal leukoencephalopathy, two of which reported a fatality.³⁷⁻⁴⁰ The manufacturer and FDA intentionally referred to the natalizumab action as a marketing suspension, as they are actively working to return the product to the market, and FDA plans to hold an advisory panel on the safety of the drug.^{41,42} Even if natalizumab were to return to the market in 2006, its diffusion is expected to be slow because of safety concerns.

Another example of safety concerns slowing drug diffusion is the heart failure therapy nesiritide (Natrecor, Scios). Since its FDA approval in late 2001 for "patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity," sales of nesiritide grew to nearly \$400 million in 2004.^{1,43} Safety concerns for nesiritide were identified in early 2005 when two systematic reviews of existing nesiritide data were published. A review that combined data from three studies found that the risk of death within 30 days after nesiritide therapy was higher than in controls who did not receive an inotrope.⁴⁴ The second study combined data from five studies and found that nesiritide-treated patients, even those treated at lower dosages, had an increased risk of worsening renal function compared with all types of control patients.⁴⁵ In addition, the growing use of nesiritide in outpatient clinics for heart failure "tune-

ups" was reported, and a prominent cardiologist implied in an editorial that the manufacturer played a role in facilitating this unlabeled outpatient use through its toll-free reimbursement hot line and billing guide.^{46,47} Questions regarding the safety of nesiritide and other issues described above have resulted in a marked decrease in expenditures for this agent in the second quarter of 2005 (Figure 1). Given these developments, nesiritide is a high-cost agent that health-system pharmacists should monitor closely for inappropriate use.

Nonetheless, the typical diffusion pattern of increasing use due to expanded indications and wider acceptance continues. Use of recombinant factor VIIa (NovoSeven, Novo Nordisk) continues to increase (Figure 2), particularly in light of new indications, such as the treatment of intracerebral hemorrhage.⁴⁸ In the first quarter of 2005, hospital and clinic expenditures for this drug were more than double the expenditures in the same time period in 2002. Another example is the increasing use of the colony-stimulating factors (CSFs) pegfilgrastim (Neulasta, Amgen), filgrastim (Neupogen, Amgen), and sargramostim (Leukine, Berlex). Figure 3 presents the growth in total hospital and clinic CSF expenditures and trends in pegfilgrastim and filgrastim expenditures for hospitals and clinics. Driven by increasing use in clinics, expenditures for CSFs increased approximately 22% from the first quarter of 2004 to the first quarter of 2005. With an increase of about 30% from the first quarter of 2004 to the first quarter of 2005, growth in pegfilgrastim expenditures in hospitals and clinics has been greatest, but filgrastim expenditures have remained stable, with only a 2.5% increase from 2004. Recent guidelines from the National Comprehensive Cancer Network recommend broader use of these drugs.⁴⁹ Based on a study published in early

Figure 1. Quarterly nonfederal hospital and clinic sales of nesiritide.¹

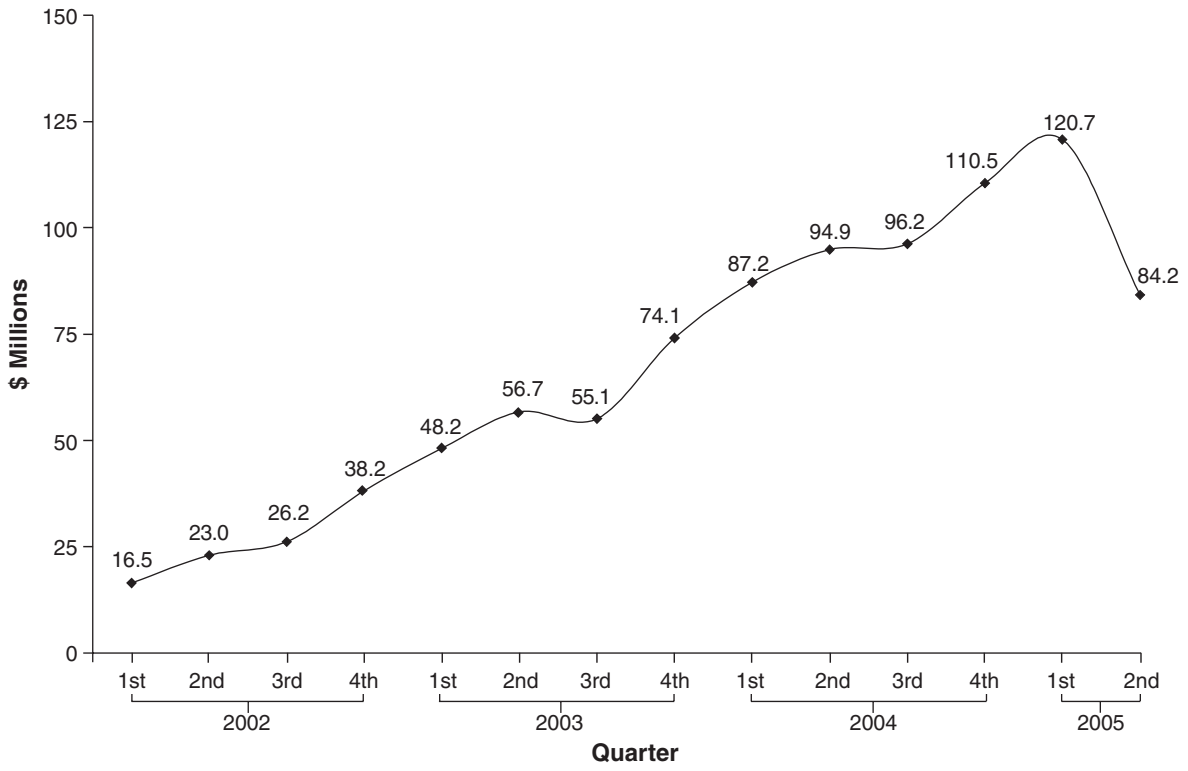


Figure 2. Quarterly nonfederal hospital and clinic sales of recombinant factor VIIa.¹

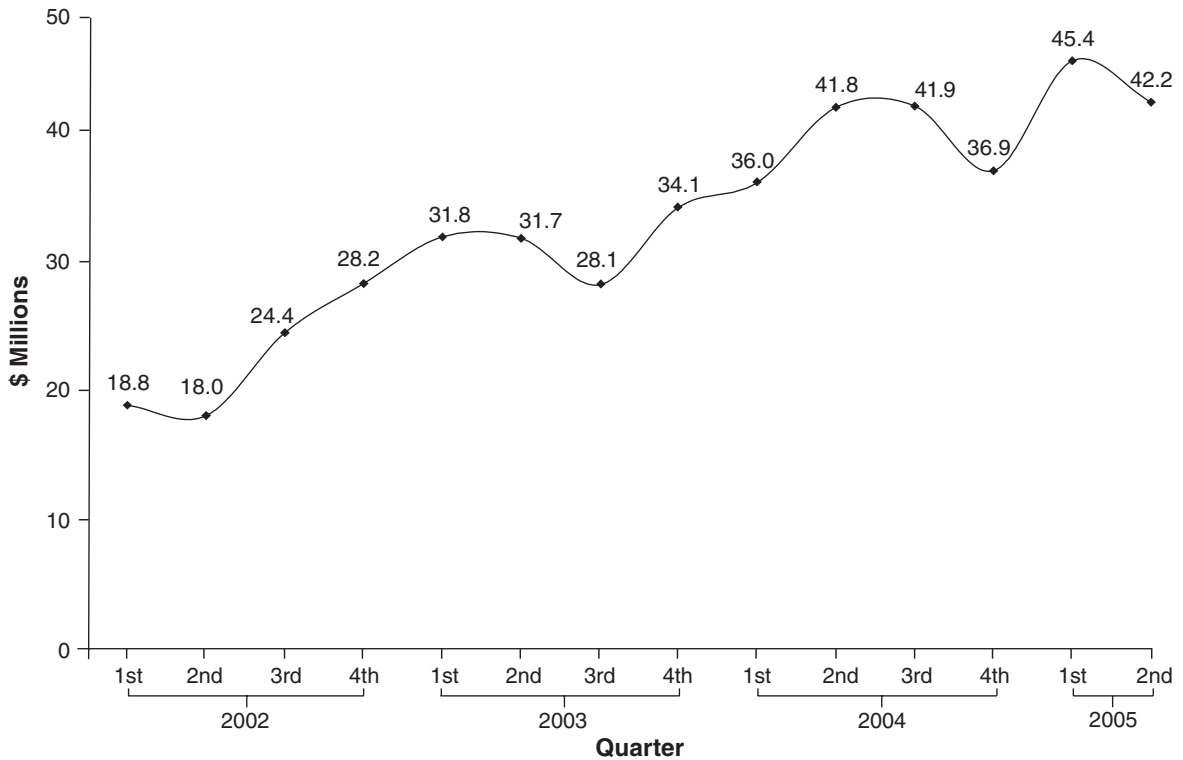
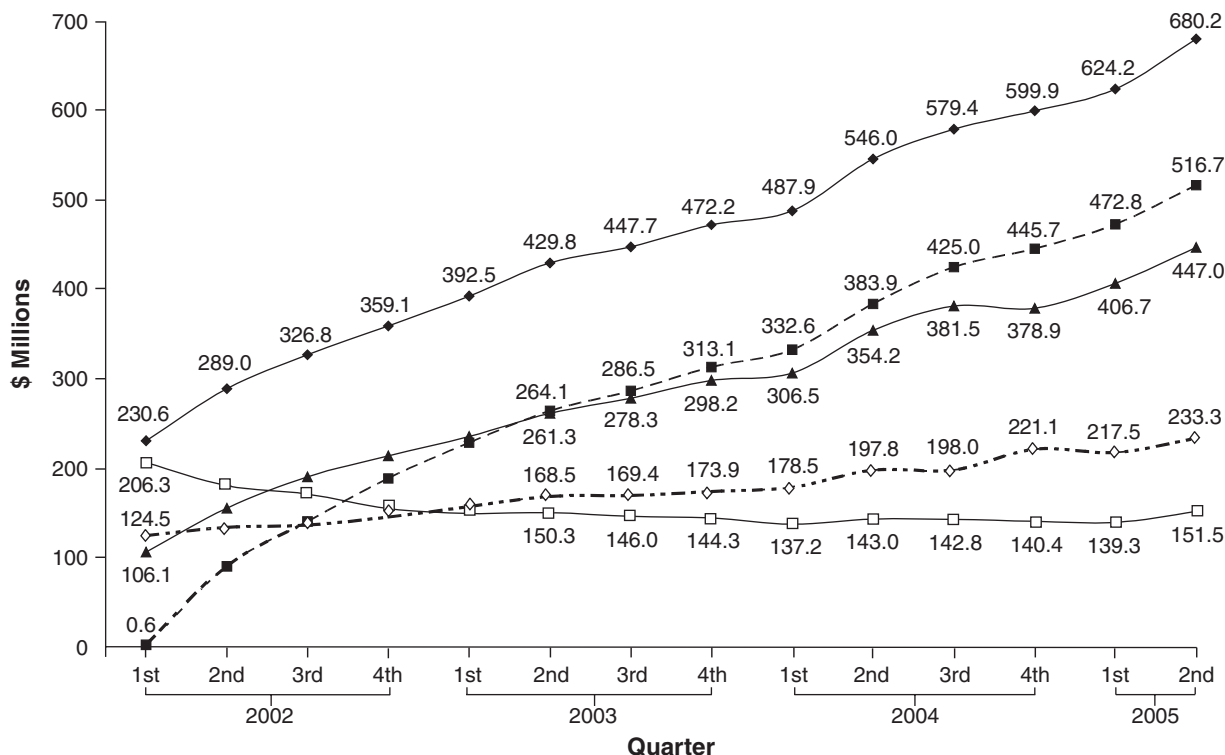


Figure 3. Quarterly hospital and clinic sales of colony-stimulating factors (CSFs).¹ Total CSFs include pegfilgrastim, filgrastim, and sargramostim. Filled diamonds = total CSF sales for hospitals and clinics, open diamonds = total CSF sales for nonfederal hospitals, filled squares = total pegfilgrastim sales for hospitals and clinics, open squares = total filgrastim sales for hospitals and clinics, triangles = total CSF sales for clinics.



2005, FDA expanded pegfilgrastim's indications to include use in less myelosuppressive chemotherapy regimens.^{50,51} A further increase in the use of CSFs is expected in 2006.

Generic drugs

Both at the national and individual health system levels, the prompt availability and subsequent widespread use of generic drugs can substantially reduce prescription drug expenditures. The savings potential with generic drugs and the importance of policies encouraging their use was illustrated by a recent analysis of outpatient drug use in a nationally representative sample of U.S. adults.⁵² The study examined the use of generic formulations and estimated potential savings that could result from broad substitution of generic drugs for equivalent brand-name products. The authors reported that greater outpatient generic drug use

in 2000 would have reduced national drug spending by \$8.8 billion, approximately 11% of total drug expenditures for the sample studied. Undoubtedly, it remains important to monitor trends related to the availability and pricing of generic drugs. Recent noteworthy developments include changes in patent law for innovator products, the continuing consolidation of the generic drug industry, and the prospects for the introduction of generic biologicals.

New legislation in Congress has the potential to significantly change U.S. patent law, including that for pharmaceuticals. The Patent Reform Act of 2005, which was recently introduced in the U.S. House of Representatives, would enact a variety of changes intended to make the U.S. patent system more efficient.⁵³ For example, the new law seeks to quickly eliminate invalid patents by setting up a postpatent opposition process.⁵⁴

In addition, current patent law favors the first to invent; the act would change the law to grant patents to the first to file a patent, which would align U.S. patent law with the rest of the world.⁵⁵ Although the Generic Pharmaceutical Association has expressed concern about the legislation, it appears that certain aspects of the legislation could improve the availability of generic drugs.⁵⁶ However, any effects of this legislation would be realized over a period of years. The most immediate patent reforms that may help improve generic access are those enacted by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, especially the provision that limits drug companies to one 30-month stay to innovator drug patents during legal challenges.⁵⁷

Generic drug manufacturing is quickly becoming a global industry dominated by several large multina-

tional corporations. Significant mergers and acquisitions in the generic drug industry were announced in 2005, and further consolidation is expected to continue through 2006.⁵⁸ The Swiss company Novartis AG, a leading generic manufacturer through its Sandoz subsidiary, acquired Eon Labs in a \$1.7 billion deal.⁵⁹ An even larger acquisition was Israel's Teva Pharmaceuticals Industries's \$7.4 billion acquisition of Miami-based Ivax Pharmaceuticals, which will make Teva the world's largest drug manufacturer.^{60,61} In a bid to enter markets in the United States and Western Europe, Indian generic firms have acquired companies throughout Europe, the United States, and Canada.⁶² Ranging in cost from \$6 million to \$268 million, these acquisitions are tiny compared with the mergers mentioned above, but they further illustrate the consolidation in the industry and its increasingly global composition.

To date, consolidation in the generic drug industry appears to have had a minimal impact on generic drug pricing. The argument can be made that fewer companies in the market will result in higher prices for generic drugs. There has been anecdotal evidence of this phenomenon occurring for specific generic drugs, particularly injectable antibiotics.⁶³ However, overall generic drug price increases were modest in the beginning of 2005, and one source even suggested that generic drug prices decreased 3% in 2004.⁶⁴

Biological therapies, such as epoetin alfa, darbepoetin, filgrastim, pegfilgrastim, and infliximab, are consistently among the top expenditures for hospitals and clinics, and equivalent generic biologicals would likely lead to important cost savings.^a While patents for some biologicals have already expired, no generic biologicals have been marketed, and the regulatory process for the approval of biological generics in the United States is unclear.⁶⁵ FDA was expected

to issue guidance on the regulatory process for biological generics, but the guidance has been delayed on several occasions. It was suggested that legislation would be needed to clarify the issue, but Congress's interest in action to address the issue has waned due to recent drug safety concerns, including the product withdrawals already discussed.⁶⁶ It appears that the regulatory pathway for generic biologicals will not be clarified for several years.

Older biologicals, such as human growth hormone and insulin products, are expected to be the first generic biologicals to reach the U.S. market. These products were approved before the Biologic Licensing Application process was established using an NDA in a manner similar to that for chemical compounds.⁶⁷ Generic forms of these products could theoretically be approved under existing regulations, and major generic firms are pursuing this approach.⁶⁸ However, an application for generic growth hormone was denied in 2004, and it appears that further regulatory action must occur before even generic forms of these older biologicals are available.

Generic biologicals are expected to cost 20–30% less than the innovator product.⁶⁹ The savings from generic biologicals will not be as substantial as the savings from small-molecule generic drugs because of the complexities of generic biological development and production. However, most biologicals are high-cost products, and these savings would still be meaningful. Although generic versions of biologicals are not expected to be available in 2006, it remains an important trend to monitor.

Drugs expected to lose their patent protection in 2006 and 2007 are listed in Table 2. Important potential patent expirations for 2006 include the antidepressant sertraline, the antiretroviral zidovudine, and the antihyperlipidemics pravastatin and simvastatin.

Another generic drug of particular interest to hospitals is the inhaled anesthetic sevoflurane. Although further litigation is possible, a generic form of sevoflurane is expected to become available in late 2005.⁷⁰ However, conversion to the generic product could be complicated, since contracts for anesthesia delivery devices are often bundled with contracts for inhaled anesthesia gases.

Other factors that may influence drug expenditures

In addition to population demographics, technology advancement, and routine economic phenomena, several emerging factors are expected to affect pharmaceutical expenditures over the upcoming year. While it is difficult to predict the impact of these factors in precise dollar amounts, pharmacy leaders should consider each factor as they prepare budgets and other strategic and tactical plans in their organizations.

Medicare Part D. The new Medicare prescription drug benefit is scheduled to begin January 1, 2006, and will eventually provide prescription drug coverage for up to 41 million seniors. The total cost of the benefit over the next 10 years, as recently estimated by the White House, is \$1.2 trillion dollars, up considerably from the \$400 billion that the President originally told Congress the program would cost.⁷¹ It is widely anticipated that the benefit will increase the overall use of prescription drugs by making them more readily available and more affordable to Medicare beneficiaries.

The impact of Medicare Part D on the price of medications is unclear. The plan includes no significant mechanisms to control drug prices; instead, price negotiations are left to the prescription drug plans that will administer the benefit. The effect of the new program on hospital medication use is equally unclear. Hospitals with large outpatient pharmacies or that operate residential-living fa-

cilities or nursing homes will undoubtedly see increases in drug utilization. The increased access to and utilization of pharmaceuticals by seniors may also carry over to hospitals as those individuals become hospitalized. Some have suggested that pharmaceutical companies will raise their prices for hospitals because of concerns about best-price issues and not wanting to establish too low of a best price.

It is also unknown how many seniors will voluntarily enroll in the Part D program. If history is any indication, the slow uptake of the Medicare drug discount cards may suggest a similar fate for the benefit itself. According to a Kaiser Family Foundation survey of seniors conducted in October 2005, only 31% had a favorable impression of the new Medicare drug benefit.⁷² When asked about their plans to enroll in the benefit in 2006, indecision (43%) and nonparticipation (37%) were seniors' most common responses. Only 20% of seniors indicated that they will enroll. Delayed or low enrollment may lessen any effect that the benefit would have on hospitals in 2006.

Emerging specialty injectable medications. Specialty pharmaceuticals have presented a major challenge in the management of drug expenditures in recent years. Specialty pharmaceuticals include biologicals, oncology agents, and high-cost injectable treatments, usually for chronic diseases. In addition, these drugs are usually i.v. infusions or injectables and often administered in the outpatient clinic setting or infusion centers. These products are used by only 0.2% of the U.S. population but account for 8% of total medical costs for every 1 million insured lives.⁷³ The average annual cost of treatment with a specialty pharmaceutical has been estimated at \$71,000 per person.⁷⁴ However, this annual cost per person can be as high as \$250,000 for a drug like imiglucerase, used for the treatment of Gaucher's disease.

Table 2.

Potential Patent Expirations, 2006–2007^a

Drug	Manufacturer	Class	Current Patent Expiration Date ^b
Ondansetron (Zofran)	GlaxoSmithKline	Antiemetic	2006
Finasteride (Proscar)	Merck	5- α reductase inhibitor	2006
Pravastatin (Pravachol)	Bristol-Myers Squibb	Antihyperlipidemic	2006
Sertraline (Zoloft)	Pfizer	Antidepressant	2006
Simvastatin (Zocor)	Merck	Antihyperlipidemic	2006
Bupropion, extended release (Wellbutrin XL)	GlaxoSmithKline	Antidepressant	2006
Zidovudine (Retrovir)	GlaxoSmithKline	Antiretroviral	2006
Zolpidem (Ambien)	Sanofi	Hypnotic	2006
Fentanyl transmucosal (Actiq)	Cephalon	Opioid analgesic	2007
Cetirizine (Zyrtec)	Pfizer	Antihistamine	2007
Amlodipine (Norvasc)	Pfizer	Calcium channel blocker	2007
Carvedilol (Coreg)	GlaxoSmithKline	β -/ α -blocker	2007
Ziprasidone (Geodon)	Pfizer	Atypical antipsychotic	2007
Sumatriptan (Imitrex)	GlaxoSmithKline	Antimigraine	2007
Pantoprazole (Protonix)	Wyeth	Proton pump inhibitor	2007

^aSource: Medications in Development Database, University of Wisconsin Hospital and Clinics.

^bPatent expiration dates were verified from multiple sources at the time of publication. Drug patent expirations are subject to rapid change, and patent expiration does not guarantee drug availability.

These drugs can significantly affect health-system pharmacy budgets in two ways. First, many of these drugs are administered in outpatient infusion centers or hospital-based clinics. Since billing and payments occur after drug administration, health-system pharmacy administrators often do not know if they are being adequately reimbursed for these drugs. Given the cost of these drugs, low reimbursement rates may negatively affect clinic drug budgets. Second, many of the patients treated with specialty pharmaceuticals have chronic diseases and are more likely to be hospitalized compared with the general population. Thus, these expensive treatments may need to be administered to inpatients as the use of these drugs increases. Hospitals need to monitor the use of these agents and may need to consider "carving out" the payment of specialty pharmaceuticals for inpatients.

A wide variety of other factors should also be monitored. For example, changes in the relationships

among manufacturers, wholesalers, and group purchasing organizations may substantially affect how the costs required to manage the pharmaceutical supply chain are paid.^{75,76} The possibility that purchasers (health care provider organizations) bear these costs, whether in a transparent fashion (in the form of fees paid to wholesalers or group purchasing organizations) or in the form of higher contract costs to manufacturers, must be considered.

Drug expenditure forecast

Forecasting pharmaceutical expenditure patterns is very complex. The factors that drive increases in pharmaceutical expenditures can be divided into four principal categories: (1) price inflation, (2) utilization, (3) drug mix, and (4) a blend of utilization and mix representing expensive but innovative medications. The inflationary rate of prescription drugs attributable to price is the increase in unit cost for existing drugs over time. The increase in expenditures attributable to utilization can

be described as the changes in number of users, number of days of therapy, or the dose per day of therapy. The increase in expenditures attributable to drug mix reflects utilization patterns that emphasize newer, more expensive agents over older, less expensive, yet equally effective alternatives (e.g., manifesting as a preference for brand-name products over generic alternatives). Finally, a portion of the increase in pharmaceutical expenditures can be attributed to a blend of the utilization and mix factors previously described. In this case, very expensive drugs become available to treat diseases that are otherwise untreatable with existing medications.

Various factors contribute to the development of a forecast for future pharmaceutical expenditures. These factors include changing patterns of prescription drug utilization, the impact of new drugs in development, expected patent expirations, and changes in price of existing drugs. Below we summarize trends in prescription drug expenditures and present specific information related to drug expenditures in clinics and hospitals. While this article is primarily directed at practitioners in hospitals and health systems, drug expenditure patterns for the outpatient and clinic settings are also discussed. We define drugs administered in a physician's office or a hospital outpatient clinic as clinic-administered drugs. Clinic-administered drugs are typically chemotherapy or biologicals that are administered intravenously. Trends in ambulatory (outpatient and clinic-administered) drug expenditures may not be relevant for health systems that do not manage significant outpatient enterprises, but they should also be considered by hospitals, as these behaviors often influence inpatient utilization. Further, outpatient drug expenditures drive public and policy-related awareness of rising drug expenditures.

Trends in overall prescription drug expenditures. Several reports are released annually studying the trends in prescription drug expenditures, as well as their drivers (Table 3).^{1,9,77,78} The Express Scripts cohort uses a substantial sample of Express Scripts clients, but excludes Medicaid recipients and Medicare beneficiaries enrolled in Medicare + Choice plans. The data reported for Express Scripts in Table 3 also excludes specialty pharmaceuticals. IMS Health data contains prescription drug sales for retail and nonretail settings. It is important to note that two of these reports (Express Scripts and Medco Health) focus solely on prescription drug expenditures in the outpatient setting and observed only a managed care population.

The methods used in each of these studies vary, and thus the estimates of overall growth in drug expenditures between 2003 and 2004 are slightly different, ranging from 8.3% to 10.6%. Price inflation was the biggest driver of the increase in drug expenditures in 2004 (for two of the three analyses), similar to the trend seen in 2003. Lipid-lowering agents were the main drivers of the overall trend and accounted for 6.6% of the total prescription drug expenditures in 2004.^{10,77,78} In addition, rheumatological drugs experienced the highest growth in both the Medco and Express Scripts populations. This trend was largely driven by the increased use of newer biological agents. All of these analyses found that drug safety concerns for COX-2-selective NSAIDs, SSRIs, and antipsychotics significantly contributed to the slowing of the inflationary trend.^{10,78,79}

Express Scripts projects a 12.0% and 11.6% increase in drug expenditures per capita in 2006 and 2007, respectively. Medco is forecasting a 10–13% increase in 2006 and 2007. IMS Health projects an increase of 7–10% in the prescription drug expenditures in 2006.¹⁰ CMS estimates that total outpatient prescription drug

expenditures will increase by 11.6% and 10.7% in 2006 and 2007, respectively.² Thus, there is some variation in the projected growth of drug expenditures. Increases in generic drug utilization, the negative impact of drug safety issues, decreases in prescription drug coverage, and higher overall utilization are expected to be the key factors in future drug expenditure trends. To date, the impact of the Medicare drug benefit and prescription drug importation on overall prescription drug expenditures remains uncertain.

Overall, spending on prescription drugs in nonoutpatient settings (hospitals, clinics, long-term-care facilities, and home health care) increased by 10% from 2003 to 2004, compared with an increase of 17.4% from 2002 to 2003.¹ These settings accounted for 27% of the total dollar volume of drug sales in 2004. Nonfederal hospitals accounted for 39% of the drug spending for the nonretail setting and 10.4% of the total drug expenditures for 2004. Trends in drug expenditures for nonfederal hospitals and clinics are described below.

Trends in clinic-administered drug expenditures. Expenditures for clinic-administered medications increased by 12.3% in 2004.¹ Growth in expenditures for clinic-administered medications was significantly greater than growth in outpatient and hospital expenditures. Clinic drug expenditures have increased by 105% over the five-year period between 2000 and 2004, increasing from \$10.7 billion in 2000 to \$22.2 billion in 2004. However, clinic drug expenditures are small in relation to total medication expenditures (representing only 9% of total medication expenditures in 2004) and largely involve Medicare-paid administration of oncology agents, a practice that could be significantly altered with changes in Medicare reimbursement for clinic-administered drugs. The continued emergence of the restricted-access programs and specialty pharmacies

Table 3.
Prescription Drug Expenditure Trends^{1,77,78}

Item	Express Scripts	Medco Health	IMS Health
Data source	Express Scripts claims data	Medco Health claims data	National Sales Perspectives
Population	Individuals in a sample of health plans served by Express Scripts (70% nonmanaged care and 30% managed care; excludes Medicaid and Medicare + Choice enrollees)	Clients with integrated benefits (plans that include both retail and home delivery options)	Total retail national pharmaceutical sales
Population size	3 million	NA ^a	Total U.S. population
Cost data	Discounted AWP	Net of AWP discounts and rebates	Invoice price
Overall increase in prescription drug expenditures, 2003–2004 (%)	10.6	8.5	8.3
Increase attributable to price from 2003 to 2004 (%)	6.0	2.9	4.6
Increase attributable to utilization from 2003 to 2004 (%)	4.3	5.4	1.6 (utilization and mix)
Increase attributable to mix from 2003 to 2004 (%)	0.3	0.2	2.1 (new drugs only)
Trend projection, 2006 (%)	12.0	10–13	7–10
Trend projection, 2007 (%)	11.6	10–13	NA

^aNA = not available, AWP = average wholesale price.

that often manage these therapies has clear practical and financial implications for health-system pharmacies, but there is not yet sufficient information to quantify the implications of these practices.

Over the past two years, hospital outpatient costs have increased more than any other component of health care expenditures,⁴ largely because of an increase in patients being treated in the outpatient setting. Similarly, there has been an increase in the diseases and number of people treated with clinic-administered medications. More cancers, often treated with high-cost medications, are also being managed in clinic settings. This trend is expected to continue as the number of cancer diagnoses grows.⁷⁹ Early signs indicate that the inflationary trend for clinic-administered medications is slowing after years of growth at an annual rate exceeding 20%. This decrease can largely be attributed to a decrease in utilization and the mix of drugs used in clinics. However, negligible price inflation for these drugs is also important to the moderate growth of drug expenditures. In 2004, all of the 12% infla-

tionary trend in clinics could be attributed to utilization and mix. The growth in utilization and mix in clinics during the first nine months of 2005 was 9% compared with the same time period in 2004. The top five drugs in 2004 accounted for 39% of all clinic-administered medication purchases, and the top three (epoetin alfa, infliximab, and darbepoetin) accounted for 29% of all purchases (Table 4).

Antiviral agents and anti-nauseants experienced the highest growth in expenditures among clinic-administered medications, increasing by 38% and 33% respectively. Growth in expenditures for antiviral agents was largely driven by an increase in expenditures for antiretrovirals. As shown in Table 4, the growth in expenditures for gastrointestinal agents was driven by infliximab (Remicade, Centocor), which had a 25% increase in sales. Growth in expenditures for blood growth factors was driven by an 84% increase in darbepoetin sales. Infliximab is classified as a gastrointestinal agent but is also used for other non-gastrointestinal indications (e.g.,

rheumatoid arthritis). Expenditure growth for oncology agents was driven by trastuzumab (Herceptin, Genentech), for which expenditures grew by over 34%, and by oxaliplatin (Eloxatin, Sanofi-Synthelabo), for which expenditures increased by over 72%. Many common oncology agents did not increase in expenditures in 2004, and expenditures for some decreased.

Over the past three years, i.v. immune globulin (IVIG) has had a significant increase in expenditures for the hospital and clinic setting (Figure 4). Quarterly expenditures increased to \$200 million in the first quarter of 2005, a 52% increase compared with \$131 million in the first quarter of 2004. Clearly, much of the growth in expenditures has taken place since the first quarter of 2004. The growth in expenditures for IVIG may be attributed to the shortages over the past year and the resulting price inflation. This growth in prices is very similar to that seen during the IVIG shortage in 1997.⁸⁰ Further, the significant decrease in reimbursement of IVIG by Medicare on January 1, 2005, makes IVIG an impor-

tant fiscal issue for patients treated in clinics.

Trends in hospital drug expenditures. Data for nonfederal hospital drug purchases taken from the IMS Health National Sales Perspectives database were used to evaluate trends in hospital drug expenditures.¹ These data consisted of drug purchasing information for 5230 hospitals in 2004. Hospital drug expenditures were \$24.7 billion in 2004, representing an increase of 7.9% from 2003. This is an increase compared with the 6.1% growth seen from 2002 to 2003. Factors affecting the trend in hospital drug expenditures included drug prices (2.6%), volume and therapeutic mix (3.1%), and new drugs (1.9%). Injectable drugs accounted for 74% (\$18.0 billion) of total inpatient drug expenditures.¹ Expenditures for injectables increased by 8.8%, while expenditures for noninjectables increased by 5.4% in 2004 from 2003. However, injectable drug prices rose at a lower rate than prices for noninjectables. Overall, drug prices for injectables increased by

only 1.1% from 2003 to 2004, while prices for noninjectables increased by 5.7%.

Table 5 presents the hospital drug expenditures and change in expenditures for the top 10 therapeutic classes. These therapeutic classes make up more than 70% of hospital expenditures. Antiinfectives alone make up almost 12% of the hospital drug expenditures. Expenditures for antiinfectives increased by 9% in 2004 and by 15.4% in 2005. Growth in antiinfective expenditures was largely driven by caspofungin, linezolid, and piperacillin-tazobactam, which increased in expenditures by 56%, 45%, and 24%, respectively, from 2003 to 2004. Diagnostic aids were the fastest-growing therapeutic class, followed by hospital solutions and antineoplastic agents.

Table 6 presents the hospital drug expenditures and change in expenditures for the top 15 drugs. These drugs accounted for 29% of total inpatient drug expenditures in 2004. The most significant growth in dollar volume in 2004 was for darbepoetin,

which increased in expenditures by 68%. However, this was offset by a significant decrease in expenditures for the epoetin products, which decreased by more than 13%. Drug expenditures for nesiritide increased by more than 63% in 2004, which was somewhat surprising given the safety concerns associated with this drug, but, as previously mentioned, expenditures for this drug decreased in 2005.

Forecast of increased drug expenditures for 2006. There may be important new drug approvals in 2006, but no drugs in the pipeline are expected to have a major financial impact across all settings. Increased utilization is expected to continue in the outpatient setting, especially with the implementation of the Medicare drug benefit. We project an inflationary rate of 7–9% for the outpatient setting (3–4% related to price, 3–5% related to volume and mix, and 1% related to new drugs). It is expected that slowdown of the drug expenditure trend for clinics will continue, particularly with the ex-

Table 4.
Top 15 Drug Expenditures for Clinics¹

Drug	Total 2004 Expenditures (\$ Thousands)	Percentage of Total 2004 Clinic Expenditures	Percent Increase over 2003	2005 Expenditures (through Sep 2005) (\$ Thousands)	Percent Increase, Year-to-Date Sep 2005 versus Year-to-Date Sep 2004
Epoetin alfa (Procrit, Epogen)	3,901,126	17.7	-0.05	2,865,673	-1.0
Darbepoetin (Aranesp)	1,214,297	5.5	83.8	1,223,798	42.0
Pegfilgrastim (Neulasta)	1,160,429	5.3	45.8	1,101,693	30.6
Infliximab (Remicade)	1,269,004	5.8	25.1	1,064,651	14.9
Rituximab (Rituxan)	950,981	4.3	12.1	864,666	24.9
Oxaliplatin (Eloxatin)	541,014	2.5	71.8	543,763	39.2
Docetaxol (Taxotere)	635,990	2.9	-0.4	502,033	4.8
Zoledronic acid (Zometa)	466,887	2.1	10.6	394,787	15.4
Trastuzumab (Herceptin)	364,762	1.7	33.9	377,999	41.1
Gemcitabine (Gemzar)	420,510	1.9	16.6	348,722	12.8
Paricalcitol (Zemlar)	349,728	1.6	23.7	281,285	7.0
Pneumococcal vaccine, diphtheria conjugate (Prevnar)	349,836	1.6	-16	270,795	3.6
Irinotecan (Camptosar)	327,023	1.5	-14.9	228,485	-8.9
Filgrastim (Neupogen)	227,999	1.0	-7.1	185,237	6.7
Carboplatin (Paraplatin)	317,603	1.4	-30.5	44,536	-86.8

pected generic availability of ondansetron. We project a 9–11% increase in drug expenditures for clinic-administered drugs (1–2% re-

lated to price, 7–8% related to volume and mix, and 2% related to new drugs). We project a 5–7% inflationary rate for hospital drug expendi-

tures (2–3% related to price, 3–4% related to volume and mix, and 1% related to new drugs). These projections are summarized in Table 7.

Figure 4. Quarterly hospital and clinic sales of i.v. immune globulin (IVIG) products.¹ Diamonds = IVIG sales for hospitals, squares = IVIG sales for clinics, triangles = total IVIG sales for hospitals and clinics.

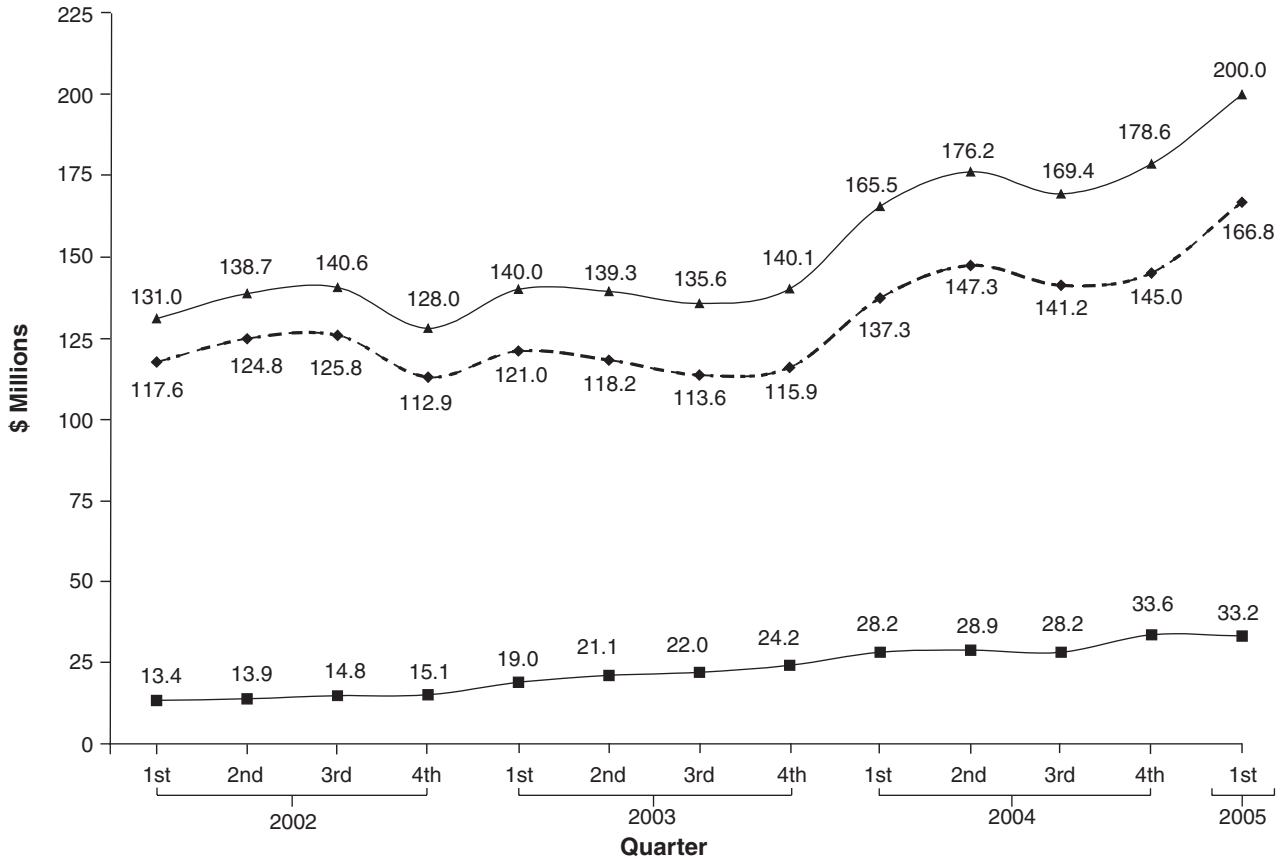


Table 5. **Top 10 Therapeutic Classes by Expenditures for Nonfederal Hospitals¹**

Drug Class	Total 2004 Expenditures (\$ Thousands)	Percentage of Total 2004 Nonfederal Hospital Expenditures	Percent Increase over 2003	2005 Expenditures (through Sep 2005) (\$ Thousands)	Percent Increase, Year-to-Date Sep 2005 versus Year-to-Date Sep 2004
Systemic antiinfectives	2,930,815	11.9	9.0	2,398,920	11.1
Hemostatic modifiers	2,745,514	11.1	9.5	2,214,756	8.5
Antineoplastic agents	2,581,121	10.4	12.9	2,042,241	5.8
Blood growth factors	2,457,858	10.0	4.4	1,955,227	6.3
Diagnostic aids	1,586,764	6.4	15.3	1,205,593	2.5
Hospital solutions	1,250,071	5.1	13.1	954,768	4.5
Anesthetics	1,107,746	4.5	5.0	889,748	9.1
Psychotherapeutics	1,114,133	4.5	5.3	845,740	1.0
Biologicals	859,399	3.5	5.7	773,072	21.8
Gastrointestinal agents	956,735	3.9	6.6	711,563	-2.4

Table 6.
Top 15 Drug Expenditures for Nonfederal Hospitals¹

Drug	Total 2004 Expenditures (\$ Thousands)	Percentage of Total 2004 Nonfederal Hospital Expenditures	Percent Increase over 2003	2005 Expenditures (through Sep 2005) (\$ Thousands)	Percent Increase, Year-to-Date Sep 2005 versus Year-to-Date Sep 2004
Epoetin alfa (Procrit, Epogen)	1,178,462	4.8	-13.2	725,073	-21.4
Enoxaparin (Lovenox)	806,156	3.3	15.1	670,288	11.3
Darbepoetin (Aranesp)	379,864	1.5	68.5	453,435	70.7
Pegfilgrastim (Neulasta)	426,804	1.7	44.0	410,938	37.8
Infliximab (Remicade)	521,449	2.1	2.6	404,426	3.7
Ondansetron (Zofran)	497,174	2.0	7.6	395,694	6.1
Rituximab (Rituxan)	451,023	1.8	7.5	359,502	7.3
Piperacillin-tazobactam (Zosyn)	396,940	1.6	24.3	351,878	20.3
Propofol (Diprivan, generics)	470,571	1.9	3.5	348,175	-1.5
Ceftriaxone (Rocephin)	444,471	1.8	-0.8	296,922	-7.6
Filgrastim (Neupogen)	335,413	1.4	-2.6	260,390	4.4
Iohexol (Omnipaque)	344,644	1.4	20.8	247,364	-4.2
Sevoflurane (Ultane)	267,090	1.1	15.0	241,211	29.0
Nesiritide (Natrecor)	372,662	1.5	63.9	235,171	-12.0
Eptifibatid (Integrilin)	312,588	1.3	5.1	233,146	0.0

Table 7.
Summary of Drug Expenditure Inflation Rate Forecast by Setting

Setting	Inflation Rate Forecast (%)
Outpatient	7-9
Clinic ^a	9-11
Nonfederal Hospitals	5-7

^aIncludes drugs administered in a physician's office or a hospital outpatient clinic as clinic-administered drugs. Clinic-administered drugs are typically chemotherapy or biologicals that are administered intravenously.

Conclusion

Forecasting and managing rising drug expenditures remains a challenge. Pharmacy managers must remain vigilant in monitoring drug costs in their health system and take a proactive role in pursuing efficient drug utilization. The dynamic health policy environment further complicates drug budgeting and must be considered, especially in integrated health systems responsible for managing inpatient, outpatient, and clinic drug costs. The comparison of health-system-specific data and trends with the national information presented in this article may provide a useful context when present-

ing institutional drug costs to senior management.

^aSince biological products cannot be replicated in the same exact way as chemical compounds, the term "generic" is not entirely appropriate. A variety of other terms are used, including "postpatent biologicals," "follow-on protein products," "subsequent entry protein pharmaceuticals," "second-generation biologicals," "biogenerics," "biosimilars," "follow-on biologicals." European regulators use the term "biosimilars," but FDA appears to prefer "follow-on biologicals" and defines such a drug as "a protein product with the same amino acid sequences and a similar enough production process and overall structure to appear on its face to be very similar to an already approved product or products." The number of different terms for generic biologicals illustrates the complexity of the issue. For simplicity, we refer to these products as generic biologicals.

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