

TOP DEVELOPMENTS

on
the

*prescription drug coverage for the
elderly and low-income Americans*

*pharmaceuticals' new role in
defense against terrorism*

patent expirations

fewer new drug approvals

some important introductions

marketplace issues

PHARMACEUTICAL LANDSCAPE 2001



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Charting the Future of Pharmacy

January 2002

Dear Friends of Express Scripts:

This is Express Scripts' third annual *Top Developments on the Pharmaceutical Landscape* report. Since our report of one year ago, we have again traveled some distance, and have experienced both imaginable and unimaginable events shaping the pharmaceutical landscape. One new component of this year's report is a "Perspectives" section, offering ideas on how developments of 2001 may impact the future.

Once again, we have looked closely at the trends of the year past and identified those we believe most significantly define the path for managing the pharmacy benefit.

Developments occurred throughout the year – affected by the actions of the Food and Drug Administration (FDA), the executive and legislative branches of the federal government – and, most unexpectedly, terrorists determined to test the mettle of Americans.

- FDA approvals of new prescription drugs were down, but those drugs approved were increasingly sophisticated and came at a higher cost.
- The year passed without a Medicare prescription benefit, and President Bush's proposed prescription discount card has been stalled by a court injunction. Pharmaceutical companies, however, have begun offering their own discount cards.
- The withdrawal of several prominent drugs has taxed the FDA's drug-approval process.
- As envelopes bearing potentially deadly anthrax spores arrived on Capitol Hill, at office buildings and in postal facilities, people across the country turned to pharmaceuticals as an integral element of the nation's defense.

I have mentioned only a few of the past year's most significant pharmaceutical developments, but in contemplating them all, one fact is overwhelmingly clear: enormous challenges lie ahead for pharmacy benefit sponsors, for those who hold responsibility for forging public policy and for consumers of prescription medications. In each case, awareness and knowledge provide the best tools for arriving at solutions. In that context, we invite you to explore with us the top pharmaceutical developments of 2001.

Sincerely,

Barrett A. Toan
Chairman and CEO

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Putting the Top Developments of 2001 in Perspective

BY RAULO S. FREAR, PHARM.D, VICE PRESIDENT,
EXPRESS SCRIPTS CLINICAL SERVICES

Three common, yet distinctly different, themes thread through the many developments on the 2001 pharmaceutical landscape: *Rising Discontent*, *Caution* and *Opportunity*.

Rising Discontent

At the end of 2001, as at the beginning, 40 million Americans – including one-third of all seniors – continue to be uninsured or substantially underinsured with respect to prescription drugs. In July, President George W. Bush put forth an initial plan for a government-endorsed drug discount card for Medicare recipients. That initiative, challenged on the grounds that it lacked legal authority, remains stalled in the courts. In the meantime, however, two U.S. pharmaceutical companies, recognizing rising public discontent, stepped forward to offer their own discount card programs. These programs, targeted to low-income populations, provide discounts on the sponsoring companies' products, thus helping to make pharmaceuticals more accessible to those who cannot afford them at full price.

Why is this significant? Most simply, because the time is right.

The presidential campaign of 2000 put the issue of equitable access to pharmaceuticals clearly on the public radar screen, and it will not disappear until the problem is resolved. The pharmaceutical industry recognizes the need for action now –

specifically, action that will forestall government-enacted price controls that would take pharmaceutical pricing out of the private sector and place it into the hands of government, the model followed by many European countries.

As we look to the future, we expect that activities begun in 2001 will lead finally to a long-term, comprehensive solution to this pressing healthcare dilemma. As an interim step, we expect additional pharmaceutical companies to bring forward programs similar to those recently introduced by GlaxoSmithKline and Novartis.

As we look to the future, we expect that activities begun in 2001 will lead finally to a long-term, comprehensive solution to this pressing healthcare dilemma.

Caution

The American ideals of "Life, Liberty and the pursuit of Happiness" were substantially challenged in 2001, perhaps to a greater extent than at any time in our history. Even before the tragic events of Sept. 11, however, issues regarding the safety and appropriate use of prescription pharmaceuticals in the United States tested the Food & Drug Administration's (FDA) drug-approval and monitoring process.

OxyContin®. Consider, for example, the indiscriminate use of OxyContin, so important to sufferers of chronic pain. By destroying its time-release properties, illegal abusers of this drug created a wave of negative publicity. Ultimately, the consequence may be intensified scrutiny of time-release products submitted for FDA approval and greater accountability on the part of manufacturers that market similar products.

Concern About Safety. Post-marketing surveillance – another mechanism of utmost importance to our approval system, which attempts to bring drugs to market in the shortest time possible – also was challenged by other events. An important case in point is new information about how the cardiovascular effects of COX-2 inhibitor drugs may differ from the effects of traditional, non-steroidal anti-inflammatory agents. In an unrelated case, the withdrawal of the lipid-lowering drug Baycol® cast in doubt the safety of cholesterol-reduction drugs. These examples point directly to the fact that side effects and toxicities of newer, safer drugs are relatively rare, and in many cases will be discovered only after large numbers of patients receive them in real-world settings. As with any medical treatment, use of prescription drugs carries both risks and benefits, and they must be weighed carefully against each other.

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FDA Approvals. At the end of 2001, one fact is especially notable: The number of innovative drugs approved for marketing in the United States has declined, compared to recent years. Is this fall-off indicative of caution on the part of the FDA? Or of a cautious metamorphosis in the drug-discovery process? Probably both. While the FDA awaits new leadership and considers whether it will adopt a new approach to the drug-approval process, pharmaceutical companies are re-examining the drug-discovery process. The industry, which was becoming a group of pharmaceutical giants, has in recent years seen the emergence of a new group of smaller biotechnology and niche drug companies. These companies are uniquely equipped to initiate the drug-development process and later establish relationships with larger, better-established firms to bring drugs to market.

We enter our new century at a critical juncture in the pursuit of pharmaceuticals to treat ever more conditions that affect

our lives. The race to understand information gleaned from the Human Genome Project will forever change how pharmaceuticals are developed. And, as new agents are discovered and put forth for approval, the question remains: How will the FDA position itself to respond to more rigorous regulatory demands?

Impact of Terrorism. Finally, the last quarter of 2001 brought still more caution from an unanticipated source. As winter approached, it wasn't the threat of rain, sleet or snow that struck fear into the hearts of the American public, but the threat of white powder. As a result, Cipro® and doxycycline have become household words. The menacing prospect of further anthrax-spore contamination and the possibility of using ion-beam radiation to sterilize the mail challenge one of the country's most venerable institutions – one that we have most often taken for granted: the United States Postal Service (USPS). Very little is known about how radiation may affect the integrity of pharmaceutical products. Express Scripts is maintaining contact with the FDA and the USPS as these agencies identify and develop procedures to ensure the safety of mailed prescriptions.

Opportunity

Despite the challenges of 2001, plan sponsors should find reason for optimism. Most notably, we are entering an unprecedented period of patent expirations for many high-use, high-cost drugs. It is true that pharmaceutical companies are defending their patent rights vigorously. Nonetheless, the door is beginning to open to more and more generic alternatives. In addition, new drug therapy classes that are likely to take over treatment of many common chronic diseases (allergy, high blood pressure, high serum lipids, asthma, gastrointestinal diseases and adult-onset diabetes) are failing to emerge from the drug-discovery pipeline.

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2001 gave us an object lesson in the potential impact of an important generic-drug introduction. Physicians and patients quickly and enthusiastically embraced generic forms of the antidepressant drug Prozac® after their introduction, and pharmacy benefit management companies in the United States have reported record rates of changeover. Within a three-month period, 90% of Express Scripts' Mail Service Pharmacy customers were using the cost-saving generic product.

The time is now right for plan sponsors to position themselves ahead of the curve by adopting aggressive programs that will encourage quick interchange to cost-saving generic alternatives as they appear on the market. Additionally, new opportunities exist to actively pursue interchanges from chemically similar agents within classes to new, less expensive generics. We have forecast a decrease in the rate that prescription drug costs will rise over the next four years, down from more than 16% to less than 12%, largely as the result of new generic availability. Rarely does the pharmaceutical landscape offer such a clear opportunity.

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Top Developments on the Pharmaceutical Landscape: 2001

Prescription Drug Coverage for Elderly and Low-Income Americans Remains on the Political Agenda

As the cost of pharmaceuticals continues to rise, increasing numbers of uninsured Americans are finding the cost of needed medications prohibitive. In 2001, the urgency to find a policy solution that would make prescription drugs more affordable for Medicare and low-income populations intensified, spawning a wide variety of public- and private-sector initiatives. A comprehensive solution, however, remains elusive.

Medicare prescription-drug discount card.

Despite strong bipartisan political support for action, Congress failed to pass legislation in 2001 that would add a prescription benefit to Medicare. Even if such a measure were enacted, a lag-time of up to two years before implementation would be likely. In July 2001, President Bush proposed an interim measure – a Medicare-endorsed prescription-drug discount card program for seniors, to be offered through competing private-sector entities, including pharmacy benefit management companies approved by the federal government. The proposal met with opposition from retail pharmacists, however, and was stalled by a court injunction. By mid-January 2002, the Centers for Medicare and Medicaid Services (CMS) is expected to forward a proposed administrative rule designed to further define program activities and to address questions regarding legal authority for this initiative.

State initiatives. Various states have taken up the challenge, seeking creative means of making prescription

drugs more affordable for those without prescription-drug coverage. Some have joined with other states to form buying coalitions that would negotiate directly with pharmaceutical manufacturers for discounted prices.

Pharmaceutical industry initiatives. At least two pharmaceutical companies have established prescription-drug card programs for low-income seniors that would provide discounts on their products. GlaxoSmithKline introduced its Orange Card in October 2001, and the following month, Novartis rolled out its CareCard.

Pharmaceuticals Become an Integral Element in the Nation's Defense

An outbreak of anthrax attacks in the aftermath of Sept. 11 moved terrorism into new, biological territory. Anthrax spores were detected in federal government buildings, private business offices and U.S. Postal Service (USPS) facilities. Reports of both inhalation and cutaneous infections, as well as several deaths, unleashed a torrent of demand for pharmaceutical protection.

Use of drugs to counter biologic attacks. The demand for ciprofloxacin (Cipro®), a fluoroquinolone antibiotic approved to treat anthrax, skyrocketed following reports of the attacks – primarily to prevent rather than treat infection. Within a short period, Cipro utilization increased 35% overall, with high regional variation. This spike returned to baseline within a relatively short time. However, as demand escalated, the Centers for Disease Control and Prevention (CDC) expressed concern about

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accelerating resistance to Cipro and urged use of doxycycline as an alternative. In addition, the CDC developed new guidelines to encourage the appropriate use of antibiotics for the prophylaxis and treatment of anthrax.

Pharmaceutical industry response. In late October, U.S. Health and Human Services head Tommy Thompson reached an agreement with Bayer regarding the price of Cipro. Bayer agreed to drop its price from \$1.77 to \$0.95 per pill on Cipro purchased by the U.S. government. We see this price negotiation as a unique agreement and do not expect that plan sponsors will benefit through other price reductions. The Average Wholesale Price for Cipro remains unchanged. The manufacturer also will triple production, producing a sufficient quantity of the drug to treat 12 million people – 100 million tablets – by January 2002.

Government actions. The delivery of anthrax spores through the mail prompted the USPS to seek means of ensuring that mail passing through its facilities is safe. The USPS announced it would purchase electron-beam irradiation technology to sterilize mail, which raised questions about the potential effect of the technology on mail-service prescriptions delivered by the USPS. Collaborative government/industry efforts have been initiated, including representatives of the USPS, the Office of Homeland Security, the FDA and Express Scripts, to ensure the continued integrity of mail-service prescriptions until the impact of this technology is fully understood.

Patents Expire, but Generics Aren't Always Immediately Available – or Inexpensive

Many high-profile drugs came off patent in 2001, paving the way for lower-priced generic versions of these medications. However, the expiration of a drug patent does

not always mean the immediate introduction of lower-priced generics. Federal law accords the first approved generic product of its type six months' market exclusivity. Lacking market competition during that time, the generic drug is typically priced only slightly lower than the branded product, and the full savings impact of the generic drug is not seen until multiple generic products become available. Pharmaceutical companies' concern about losing revenue from highly successful products is another factor affecting pricing in relation to generics. This concern has led manufacturers to aggressively defend patent rights.

Major Patent Expirations and New Generics

- **Prozac® (fluoxetine).** Barr Laboratories received six months' exclusivity for its 20mg fluoxetine capsule and entered the market immediately after the patent on Lilly's blockbuster antidepressant, Prozac, expired on Aug. 2, 2001. The impact of the Prozac patent expiration was significant, with generics controlling greater than 75% of overall fluoxetine prescriptions three months after their introduction. The full financial impact of generic fluoxetine will not be seen until February 2002, when multiple generics enter the market. Prozac had \$2.2 billion in U.S. sales in 2000.
- **Pepcid® (famotidine).** The FDA approved generics by multiple manufacturers in April 2001 to compete with Merck's H-2 blocker, which had \$755 million in U.S. sales in 2000. Generics for Pepcid now represent greater than 85% of all famotidine prescriptions.
- **Mevacor® (lovastatin).** In July, Merck won a court-ordered six-month patent extension for its cholesterol-reducing drug Mevacor by submitting to the FDA a supplemental new drug application based

on new pediatric studies. The drug's patent extension expired Dec. 15, 2001. Sales of Mevacor account for only 1.5% to 2% of the statin market, while competitors Lipitor® (atorvastatin) and Zocor® (simvastatin) command 44% and 21%, respectively.

Generics Delayed from Market Entry

- **Prilosec® (omeprazole).** With sales reaching \$4.23 billion in 2000, AstraZeneca's heartburn and ulcer drug Prilosec is the world's top-selling prescription drug. The main patent covering the drug's formulation expired Oct. 5, 2001, and AndrX announced on Nov. 19, 2001, that it had received FDA approval to market its generic version of the drug. AstraZeneca challenged the expiration date in court, however, and the matter went to trial on Dec. 6, 2001. The trial is ongoing as of this writing. If and when the generic is available, we expect a rapid shift from branded Prilosec to generic omeprazole. As we have seen with other generics, savings will be fully realized when multiple generics become available.
- **Glucophage® (metformin).** Although Bristol-Myers Squibb's patent on Glucophage expired in September 2000, the manufacturer contested the patent expiration on the basis of pediatric labeling changes. The company claims these changes provide an additional three years of patent protection, rather than the usual six-month extension granted by the FDA. In December, Congress passed the *Best Pharmaceuticals for Children Act*, which reinforces the incentive for drug companies to test their products for use in children. The legislation reauthorizes the provision in the *Food and Drug Administration Modernization Act of 1997* that extends market exclusivity for six months on the basis of pediatric

testing. It does not, however, allow for the additional three years of patent protection sought by Bristol-Myers Squibb. Barring any legal action taken by Bristol-Myers Squibb, we expect generic metformin products to be on the market in early 2002.

- **BuSpar® (buspirone).** The patent for Bristol-Myers Squibb's antianxiety medication BuSpar expired Nov. 21, 2000, but the company submitted a new patent application only hours before the expiration went into effect, forcing the FDA to delay approval of competing generics. Mylan, seeking approval of its generic version of BuSpar, took the matter to court. In March 2001, Mylan received a ruling requiring Bristol-Myers Squibb to withdraw its bid for a patent extension and ordering the FDA to proceed with approval review of generics in varying strengths from Watson, Par and Mylan. These were approved in March 2001. BuSpar's U.S. sales in 2000 were \$667 million. By November 2001, Express Scripts statistics showed an 80% shift to generics. The full financial impact will be seen only after the generic marketing exclusivity period expires and competition increases.

Fewer New Drugs Are Brought To Market

In 2000, the FDA approved 27 New Molecular Entities (NMEs). By the end of 2001, 23 NMEs had won FDA approval, a decrease of 15% from the previous year. Although some drug companies have complained that the FDA is taking longer to review new medicines, government records do not support this contention. Several factors, however, contribute to the perception that the FDA is acting more cautiously.

Increased safety concerns. Several high-profile drugs that were approved in recent years, including Baycol[®], Propulsid[®], Lotronex[®] and Rezulin[™], recently were removed from the market due to associations with adverse events. As a result, the FDA may be taking a more cautious approach to pre-approval review. A number of drugs have been delayed because of concern about side effects that appeared in clinical trials and the need for more data to document safety. Among the delayed drugs: Zelnorm[™] for irritable bowel syndrome, Exubera[™] for diabetes, Xolair[™] for respiratory diseases and Ketek[™] for bacterial infections.

Manufacturing issues. A number of pharmaceutical manufacturers experienced delays in new drug development or FDA approval in 2001 because of inadequate manufacturing processes at their factories. The most notable drug to be delayed was Clarinex[®], a non-sedating antihistamine from Schering-Plough that was expected on the market by early 2001 but was finally approved on Dec. 21. While Clarinex itself was not thought to be affected by inadequate manufacturing processes, the FDA decided to withhold approval of Clarinex until Schering-Plough addressed other manufacturing processes throughout the company.

Absence of FDA leadership. At the end of 2001, an FDA Commissioner has yet to be named. The agency has been operating without a commissioner since President Bush took office in January 2001. The consequence of this extended vacancy is that the agency lacks guidance in decision-making and leadership in its dealings with manufacturers and lawmakers.

Despite Fewer Approvals, Several Important Drugs Were Introduced

While 2001 was not especially notable for the number of novel, breakthrough drugs appearing in the marketplace, the FDA approved several important drugs.

Aranesp[®] (darbopoetin). Approved in September for treatment of anemia associated with renal failure, Amgen's Aranesp is a long-acting version of Epogen[™]. While Epogen is typically taken one to three times weekly, Aranesp only requires administration once every one to two weeks, and efficacy is similar. Both drugs may be self-administered by subcutaneous injection. Shortly after initial approval, Amgen submitted additional information supporting the drug's use for treating anemia associated with cancer, which could result in significant future growth. Combined sales for Epogen and Procrit[®], an alternative therapy, were expected to approach \$5 billion in 2001.

Bextra[®] (valdecoxib). The latest COX-2 inhibitor to enter the marketplace is Bextra, from Pharmacia. Bextra was approved in November 2001 for pain associated with arthritis and dysmenorrhea. While clinical differences between Bextra and the other approved COX-2 inhibitors, Celebrex[®] and Vioxx[®], appear to be minor, the ultimate success of the drug may be in its positioning by its manufacturer. Pharmacia now has two COX-2 inhibitors on the U.S. market and may be able to position them for different patient populations. Express Scripts data shows that COX-2 inhibitors account for 44% of non-steroidal anti-inflammatory drug prescriptions and 63% of the costs.

Gleevec® (imatinib mesylate). Novartis' novel therapy for the treatment of Chronic Myeloid Leukemia (CML), approved in May, is a "smart" drug that selectively targets the disease-causing protein. Since it targets only the biological properties of cancerous cells, it does not damage healthy cells, unlike conventional cancer therapies. It will likely be a lifelong therapy for those for whom it is prescribed. CML is estimated to affect approximately 5,000 patients in the United States each year. The monthly Average Wholesale Price cost of therapy can reach as high as \$3,543, depending on the stage of the disease. The potential of Gleevec to treat certain gastrointestinal and brain tumors also is being studied.

Kineret® (anakinra). Developed by Amgen, this injectable biotech product helps decrease the symptoms of rheumatoid arthritis by blocking the effects of the inflammatory mediator, interleukin-1. Administered daily, it is likely to be prescribed for use in combination with methotrexate for patients who do not respond to other therapies or to methotrexate alone. Approximately 1% of the U.S. population is affected by rheumatoid arthritis (RA). Like other biotech products approved for RA (Enbrel®, Remicade®), Kineret is expensive, costing up to \$11,000 per patient per year. Although the RA market is rapidly expanding, we do not expect a significant expansion of drug expenses for RA products due to Kineret.

PEG-Intron™ (peginterferon alfa-2b). Schering-Plough received approval in January for its chronic hepatitis treatment, PEG-Intron. In August, the drug was also approved for use in combination with the company's Rebetol® (ribavirin). PEG-Intron is a longer-acting version of Intron® A, which is typically administered three times weekly for chronic hepatitis. PEG-Intron is administered once weekly. We expect per-member-per-year costs to increase from \$3.60 in 2001 to \$5.29 in 2002.

Rebetol® (ribavirin). Schering-Plough introduced Rebetol as a stand-alone product in 2001. Rebetol was previously available only as part of the Rebetron package. It can now be given with either Intron A or PEG-Intron for the treatment of hepatitis C. The availability of Rebetol as a single-entity product has a significant impact on the uptake of PEG-Intron, as our forecast above indicates. Additionally, the cost of treatment for a typical patient increases significantly, from approximately \$750 per month with Rebetron to between \$1,100 and \$1,200 for PEG-Intro plus Rebetol.

Multiple Events Create Potential Marketplace Issues

Several events occurring in 2001 have not yet fully played out, and their ultimate impact on utilization and cost trends will not be fully known until 2002 or even later.

The question of OTC status for Claritin®, Allegra® and Zyrtec® may be decided by the FDA – or the courts. In May, the FDA's Nonprescription and Pulmonary advisory committees reviewed a petition arguing that second-generation antihistamines Claritin, Allegra and Zyrtec, used to treat seasonal allergic rhinitis, could safely be made available as OTC drugs. The reviewing committees agreed. Not surprisingly, the manufacturers of these agents, all of which have been on the market eight years or less, oppose their redesignation as OTC drugs. Annual U.S. sales are \$1.85 billion for Claritin, \$883 million for Allegra and \$699 million for Zyrtec.

Claritin will be the first to come off patent in December 2002. The FDA appears to have the authority to redesignate these prescription antihistamines as OTC drugs, even before patent expiration. What is unclear is whether the FDA can

force the manufacturers, who own the patents protecting their products, to sell them OTC. Historically, the FDA has never forced a prescription-to-OTC switch over a manufacturer's objection. If the agency attempts to do so in this instance, the manufacturers will likely challenge the action in court.

FDA approval of Synthroid® as a new drug remains in question. Abbott's Synthroid (levothyroxine sodium), used to treat hypothyroidism, has been on the market for 42 years and is used by 8 million people. Until recently, however, levothyroxine products were not formally approved by the FDA because they were marketed before 1962, when the *Food, Drug and Cosmetic Act* was amended to require more rigorous drug testing, including efficacy as well as safety. In 1997, the FDA announced that levothyroxine products were to be considered new drugs. Manufacturers of such products would either have to submit a new drug application (NDA) or a citizen's petition justifying why an NDA should not be required. Two manufacturers chose to submit an NDA, and their drugs, Unithroid® (Watson) and Levoxyl® (King) were given final approval. Abbott chose to file a citizen's petition. In April 2001, the FDA denied Abbott's citizen's petition, and the company filed an NDA on Aug. 1, 2001. On Aug. 14, the FDA decided to begin limiting distribution of unapproved levothyroxine products, with the goal of removing any unapproved products from the market by Aug. 14, 2003.

Synthroid continues to be the market leader for levothyroxine products, with greater than 50% market share. It is significant that no levothyroxine product has been determined to be bioequivalent, and therefore interchangeable, with another, including Synthroid. Therefore, if Synthroid is not approved as a new drug, patients will need to be switched and additional lab tests may be necessary.

Cardiovascular safety of COX-2 inhibitors being debated. Two cyclooxygenase-2 (COX-2) inhibitors, Celebrex® and Vioxx®, are currently on the market, and a third, Bextra®, will join them early in 2002. Used for management of pain, these drugs have been shown to have a possibly improved gastrointestinal (GI) safety profile compared to non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, diclofenac and naproxen. However, an article in the Aug. 22-29 issue of the *Journal of the American Medical Association* raised fresh concerns about the cardiovascular safety of COX-2s. Unclear at this time is whether this finding will prompt further studies, lead to another labeling change, or impact prescribing of COX-2s, which have consistently ranked among the most-prescribed medications since their introduction in 1999. Although utilization of COX-2s plateaued after this article was published, recent data suggests utilization is approaching previous levels. COX-2 inhibitors continue to penetrate the NSAID market, with per-member-per-year costs of COX-2s projected to exceed \$17 in 2001. This amount would represent approximately 60% of the total NSAID/COX-2 market. By comparison, the entire NSAID class had a per-member-per-year cost of \$12.88 in 1998, which was the year before COX-2 inhibitors were introduced.

New NCEP guidelines for high-cholesterol management open potential for more aggressive therapeutic approaches. In May, the National Cholesterol Education Program (NCEP) issued major new practice guidelines for the prevention and management of high cholesterol in adults – the first since 1993. Important recommendations include greater attention to use of a lipoprotein profile as a diagnostic tool, sharper focus on identifying those at high risk for heart attack and heart disease (including low HDL levels), treatment of high triglycerides, and more aggressive treatment to lower cholesterol. New guidelines are expected to expand the

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number of Americans on dietary treatment from 52 million to approximately 65 million. According to the National Institutes of Health, the number of Americans on cholesterol-lowering drugs is likely to nearly triple, from roughly 13 million to 36 million.

The new guidelines emphasize drug treatment in a larger population of people; however, we believe that currently accepted treatment strategies for high cholesterol had evolved prior to release of the NCEP guidelines in 2001, and this was taken into account when we forecast annual drug trend. We are, however, still forecasting double-digit annual growth in this market over the next five years.

Illegal abuse threatens accessibility of OxyContin®. OxyContin, manufactured by Purdue Pharma, is the best-selling narcotic pain medication in the United States, with annual sales of approximately \$1 billion. It is often prescribed for patients suffering from severe pain when around-the-clock pain management is needed for an extended period. Unfortunately, a significant number of cases of illicit use of OxyContin have been documented. In 2001, a new warning was added to its label, advising prescribers of the potential for abuse and reinforcing appropriate prescribing indications. In addition, distribution of 160mg OxyContin, the highest strength available, was suspended. Recent media reports indicate that a number of

pharmacies are refusing to stock the drug, making it unobtainable by many people for whom it has been legitimately prescribed. This unfortunate development points to the importance of physician, pharmacist and patient education programs to ensure the continued availability of this and similar products for patients who need pain relief.

Withdrawal of Baycol® raises questions about the safety of statins.

In 2000, Bayer's statin drug Baycol hit \$221 million in retail sales and won an approximate 7% share of the cholesterol-reducing prescription drug market. Then, on Aug. 8, 2001, Bayer voluntarily withdrew the drug from the market following reports of severe adverse reactions, specifically, rhabdomyolysis (muscle-cell breakdown). Such reactions, which occurred more frequently when the drug was combined with gemfibrozil (Lopid®; generics), a nonstatin drug that lowers blood triglyceride levels and cholesterol, included a reported 52 deaths. Although similar reactions have been reported with all other statins, the incidence of associated fatalities was significantly higher with Baycol. The withdrawal of Baycol may cause the FDA to examine statins and their side-effect profiles more closely, including those in clinical development. Despite this safety concern, we expect a continued increase in the utilization of statins due to the new NCEP guidelines.

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