



## **2000: Top Developments on the Pharmaceutical Landscape**

### ***The Federal Government Assumes a Greater Voice in Healthcare.***

#### **New Regulations Tighten the Use of Medical Data...and Raise the Specter of New Costs.**

To prevent unethical disclosure or misuse of electronically stored personal health information, the Department of Health and Human Services embarked in 2000 on a substantial revision of regulations governing how such information may, and may not, be used. New privacy rules, adopted under the Health Insurance Portability and Accountability Act (HIPAA) on December 28, 2000, will be phased in over a two-year period, beginning in February of this year.

Under the new rules, benefit plan sponsors, physicians, pharmacies, hospitals and other organizations will need to rigorously examine the practices they employ in using and disclosing healthcare data of identifiable individuals.

The rules are extremely complex and long (the rule, preamble and comments include over 1500 pages). They will essentially apply to all individually identifiable health information ("Protected Health Information") transmitted or maintained (regardless of form) by "covered entities." Covered entities include health plans, health care clearinghouses and health care providers who transmit health information in electronic form in connection with financial or administrative activities related to health care. The final rule also requires that covered entities impose certain contractual requirements on "business associates."

Under the final regulations, health care providers who have a direct treatment relationship with an individual must, subject to certain narrow exceptions, obtain consent prior to using or disclosing Protected Health Information for treatment, payment or health care operations. For uses or disclosures of protected health information that do not involve treatment, payment or health care operations, the final rule requires that covered entities obtain a valid patient authorization.

The rules also govern how much information can be used or disclosed—covered entities must make reasonable efforts not to use or disclose more than the "minimum necessary" to accomplish the purpose for such use or disclosure. The rules include detailed guidance on the "minimum necessary" standard and specifically provide that disclosures to or requests by health care providers for treatment purposes are not subject to the minimum necessary standard.

By estimates of some national healthcare consultants, the cost of retooling systems to comply with the new rules could well exceed that expended by healthcare companies on Y2K compliance.

### **Rising Costs Drive Concern About Access and Affordability to the Top of the American Political Agenda.**

The cost of prescription drugs and affordability of healthcare captured the attention of lawmakers across America. Proposals for a prescription benefit plan for seniors have proliferated in Congress, but consensus has proved elusive. Some believe coverage should be universal, while others think eligibility should be limited to lower-income seniors. Some prefer a drug benefit offered through private-sector insurers; others argue that a prescription benefit should be added to Medicare.

At the state level, initiatives were advanced on several fronts, including efforts to statutorily restrict the price of drugs and to expand access to pharmaceuticals for low-income seniors through state-based subsidy programs. The Maine Legislature nearly enacted a price-control bill designed to increase access to prescription drugs for the uninsured. A more scaled-back drug discount program was eventually approved, which is being legally challenged by manufacturers. Eleven additional states passed legislation to establish or expand senior pharmaceutical assistance programs.

What difference will the final form of a Medicare drug benefit make to pharmacy benefit sponsors? By far, seniors consume more prescription drugs than any other segment of the population. If a drug benefit is offered through a government program, plan sponsors could see their costs reduced. On the other hand, if governmental pressure forces pharmaceutical manufacturers to lower retail prices, private plans may find their ability to negotiate rebates and other discounts eroded.

### **The Extent of Medical and Prescription Errors Becomes a National Issue...and Stirs the White House to Action.**

The National Academies Institute of Medicine (IOM) report "To Err is Human: Building a Safer Health System" revealed a highly disturbing problem: as many as 98,000 deaths a year occur in hospitals, caused by medical error. And 7,000 of those deaths involve prescription errors.

Former president Bill Clinton quickly launched a plan to reduce medical errors by 50 percent over the next five years. Responsibility for further development and execution of the plan now resides with President George W. Bush. Recommendations of the Clinton initiative include:

- Implementing mandatory error-reporting guidelines for mistakes causing death or serious injury and voluntary reporting of errors resulting in lesser consequences and close calls
- Redesigning packaging and renaming drugs to help eliminate confusion of "look-alike" and "sound-alike" drugs

- Requiring hospitals eligible to receive Medicare payments to develop and implement error-reduction plans
- Encouraging health systems to develop and implement post-error review processes
- Changing drug labeling to a more user-friendly format

Benefit plan sponsors must welcome the prospect of fewer errors, which can only mean reduced medical costs and, most importantly, vastly improved quality of care for members.

***The Pharmaceutical Industry Wins Some...and Loses Some.***

**Direct-to-Consumer Advertising Proves Its Power to Influence Prescription Drug Consumption.**

In 1999, drug companies spent \$907 million in the first half of the year to advertise their products. Over the same period in 2000, they ratcheted direct-to-consumer (DTC) advertising spending up to \$1.3 billion — the amount spent on DTC advertising for all of 1998. Why? Quite simply, it's a very good return on investment. When the final numbers are in, spending on DTC advertising for 2000 is expected to surpass the \$2 billion mark — an amount equal to only two percent of the total annual expenditure for prescription drugs.

	Top 10 DTC products, 2000 (January through June)	Jan-June 2000 DTC spend	1999 DTC rank	Total 1999 DTC spend
1	Vioxx® (rofecoxib – Merck)	\$94.6 million	N/A	N/A
2	Claritin® (loratadine – Schering)	\$66.8 million	1	\$137.4 million
3	Prilosec™ (omeprazole – AstraZeneca)	\$62.2 million	4	\$79.5 million
4	Viagra® (sildenafil – Pfizer)	\$53.5 million	3	\$79.5 million
5	Xenical® (orlistat – Roche)	\$50.2 million	5	\$75.6 million
6	Paxil™ (paroxetine – GlaxoSmithKline)	\$47.1 million	N/A	N/A
7	Celebrex™ (celecoxib – Pharmacia)	\$41 million	N/A	N/A
8	Propecia® (finasteride – Merck)	\$40 million	2	\$99.7 million
9	Flonase® (fluticasone – Glaxo Wellcome)	\$39.2 million	10	\$53.5 million
10	Zyrtec® (cetirizine – Pfizer)	\$38.3 million	6	\$57.1 million

N/A: 1999 data not available for drugs not in the top 10

Drugs in the Top 10 for 1999, but not 2000: Lipitor (#7, \$55.5 million), Zyban (#8, \$54.8 million), Nolvadex (#9, \$54.5 million).

Along with increased media coverage of new drugs and unprecedented access to drug information on the Internet, DTC advertising is a potent factor in the emergence of a

growing consumerism among plan members — a force plan sponsors can ill-afford to ignore.

This shift to consumerism is significant not only in media but in content as well. Previously, print advertisements focused on the drug. Today, television advertisements focus on a disease or condition message, and only peripherally mention the drug product, in much the same manner as traditional consumer advertising. In one recent survey, 19 percent of respondents indicated that they had asked their physician for an advertised drug.<sup>1</sup> Remarkably, in the same study, 15 percent of respondents indicated that they would switch physicians if not given the prescription. Clearly, DTC advertising has increased the demand for prescription medications.

<sup>1</sup>*Health Affairs* 19(2): 110-28.

Members' greater awareness of prescription drugs, together with their desire for access and choice, will certainly influence their perception of plan-design changes. In addition, DTC advertising encourages increased consumption, heightening the importance of appropriate utilization. Express Scripts continues to develop and recommend utilization-management measures such as step therapy, plan design options, physician and member counseling, and formulary-management strategies.

### **New Drugs Emerging From the Pipeline in 2000 Failed to Fulfill Expectations.**

A relatively steady parade of blockbuster drug launches has proved highly profitable for manufacturers — and for investors. As a result, manufacturers often promote their pipeline drugs in press releases and annual reports, building expectation of above-average financial performance.

Clinical trials, however, present stiff hurdles that any drug must clear to gain Food and Drug Administration (FDA) approval and ultimate entry into the marketplace. In 2000, a number of highly anticipated drugs hit significant roadblocks on the approval track. Some will take longer to get to market, and others may never win FDA approval.

Three highly publicized drugs, all temporarily knocked out of the running in the pharmaceutical sweepstakes, are slated for further trials:

- *Vanlev<sup>TM</sup>*, from *Bristol-Myers Squibb*. Expectations of sales for this hypertension treatment, estimated in the billion-dollar range, dimmed when clinical trials revealed its use may cause angioedema, a potentially severe side effect. Other hypertension therapies are readily available, and Vanlev, if approved in 2001, is unlikely to significantly impact plan costs in the near future.

Bristol-Myers Squibb's Vanlev<sup>TM</sup> (omipatrilat) has been positioned as a potential blockbuster medication for the treatment of hypertension. The company submitted a new drug application (NDA) with the FDA for approval of Vanlev, but withdrew it in April 2000 in response to concerns over the incidence of a potentially serious side effect, angioedema. A new study of Vanlev is currently in progress. The results of the study are expected to be available in the summer of 2001. Express Scripts expects a resubmission to the FDA for approval at that time.

- *Uprima*<sup>®</sup>, from TAP Holdings (Takeda Chemical Industries and Abbott Laboratories). Also sidelined by reported side effects, Uprima had been billed as competition for Pfizer's popular erectile-dysfunction drug *Viagra*<sup>®</sup>. Plans covering *Viagra* will probably also cover Uprima, if approved. Express Scripts' analysis of clinical trial data suggests Uprima is unlikely to offer any significant advance over *Viagra* in the treatment of erectile dysfunction.

Since Uprima is administered under the tongue, the onset of effect is more rapid than with *Viagra*. Following reports of adverse events, including nausea, fainting, and dizziness, TAP withdrew the NDA from the Food and Drug Administration to conduct further studies.

- *Pleconaril*, from ViroPharma. Billed as a cure for the common cold, this drug failed to show that its use shortens duration of symptoms. If further trial results are positive, pleconaril may be on the market in 2002.

Study results released in April of 2000 failed to demonstrate a significant reduction in the duration of colds in treated patients. In other studies, Pleconaril was evaluated for the treatment of meningitis in children, but did not demonstrate a significant effect on the reduction of time to complete resolution of headaches. Additional studies in meningitis and the common cold are currently underway, with results expected later this year.

### ***FDA Actions Both Expand and Limit Treatment Options.***

#### **New Product Approvals Bring New Hope...and Controversy.**

Among the many new drugs approved by the FDA in 2000, a number offer first-time therapies for some conditions.

- *Visudyne*<sup>™</sup>, for example, is the first drug therapy approved for treatment of patients with wet-form, age-related macular degeneration — a condition that causes blindness in approximately 200,000 Americans every year. It prevents progression of the disease in about two-thirds of patients treated, a 50-percent improvement over laser therapy alone.

*Visudyne* is administered by the intravenous route and followed by shining a non-thermal laser into the patient's eyes.

- *Zyvox*<sup>™</sup> introduces a new class of antibiotics known as oxazolidinones and is effective in treatment of bacterial infections caused by Gram-positive bacteria, including those resistant to current therapies. Available in both intravenous and oral therapies, it may decrease the length of hospitalization and the need for intravenous therapy at home.

In addition, *Mifeprex*<sup>™</sup>, better known as RU-486, or the abortion pill, was approved for the American market in 2000 after years of controversy. According to the *Wall Street Journal* (9/28/00), availability of the pill is unlikely to increase the total annual number of

abortions, but, based on European experience, fewer surgical abortions will be performed.

Both Visudyne (cost: \$4,000 per year, including laser use) and Mifeprex (cost: \$300 for a course of therapy) are administered in a clinic setting and thus will not impact the pharmacy benefit. The cost of Zyvox is \$100 a day, but shorter hospital stays and the potential for conversion from infusion to oral therapy at home should help to decrease costs.

### **New Indications May Expand Utilization and Increase Costs.**

A number of drugs already on the market received FDA approval for new indications, including some conditions for which no approved treatment previously existed. New indications enable manufacturers to target new markets for their products. Increased usage may greatly increase costs to pharmacy benefit plans, although the potential for cost increases varies with the drug.

- *Tamiflu*<sup>TM</sup>, approved a year earlier for treatment of influenza symptoms, received approval for prevention of flu. While flu vaccine will remain the standard preventative therapy, Tamiflu may be appropriate for patients for whom the vaccine is contraindicated or those at high risk for morbidity who have not had a flu shot. Growth in utilization should be modest.

Tamiflu and a similar drug, Relenza®, belong to a class of medications known as neuramidase inhibitors. Relenza is not approved for the prevention of influenza.

Tamiflu's new prevention indication will be promoted to physicians, but not to consumers. A seven-day course of Tamiflu for the prevention of influenza costs \$41.68 (AWP – Red Book, November 2000 update). Express Scripts' per-member-per-month costs for Tamiflu were \$0.03 in the first quarter of 2000.

- *Enbrel*<sup>®</sup> and *Remicade*<sup>®</sup>, both rheumatoid arthritis treatments, gained new indications — Enbrel as a first-line therapy for rheumatoid arthritis and Remicade for treatment of signs and symptoms of the disease, as well as joint damage. Plans that cover Enbrel may expect some increase in drug spend and wish to consider utilization-management protocols. Because Remicade is normally administered in a clinic setting, cost increases will usually be experienced in the medical, not the pharmacy, benefit.

However, for the next twelve months, the demand for Enbrel is expected to exceed the supply. (The limited availability of Enbrel may cause the use of Remicade to grow.)

Plan sponsor costs for Enbrel are projected to increase from \$1.17 per member per year in 1999 to \$2.14 for the year 2000. Additional cost increases, due to the new indication, are expected in the coming year.

- *Fosamax*<sup>®</sup> is the first treatment for osteoporosis in men. An estimated two million men are afflicted with this condition, and that number could increase by 20 percent over the next 15 years. Express Scripts forecasts that drug spend for osteoporosis

treatment will increase by 30 percent annually over the next five years. With this introduction, plans that presently enforce gender limitations on coverage for osteoporosis treatment should reconsider their policy.

With this new indication, Fosamax is the first bisphosphonate indicated for the treatment of osteoporosis in men. Worldwide sales for Fosamax are estimated to reach \$1.3 billion in 2000, increasing to nearly \$2.15 billion in 2003.

- *Sarafem*<sup>™</sup>, now approved for treatment of premenstrual dysphoric disorder, shares its active ingredient with the antidepressant Prozac<sup>®</sup>. In light of the upcoming expiration of Prozac's patent and the common off-label use of other selective serotonin reuptake inhibitors (SSRIs), plans will likely experience little increase in costs due to Sarafem.

### **Withdrawal of Some Drugs Leaves a Therapy Void.**

Several high-profile therapies were withdrawn from the market in the wake of identified health risks, in some cases leaving physicians with few treatment alternatives. The detection of health risks after marketing approval may point to inadequacies of clinical trials, resulting in a slowing of the drug-review process and fewer drug approvals in the near term.

- *Lotronex*<sup>®</sup>. The only drug approved for irritable bowel syndrome (IBS), Lotronex was withdrawn in 2000. Until approval of new therapies, expected in mid-2001, former Lotronex users will likely revert to earlier therapies, primarily less expensive over-the-counter products.

Lotronex was positioned as being a potential blockbuster drug with sales of \$1.5 billion to 2 billion dollars by the year 2005. Despite labeling changes and the required dispensing of a Medication Guide to patients describing the signs and symptoms of the adverse reactions, reports of adverse events continued and the drug was removed from the market.

Express Scripts' initial projections of significant increases in drug costs for treatment of irritable bowel syndrome will not be seen. Express Scripts expects PMPY drug costs for the treatment of Irritable Bowel Syndrome to remain constant until the introduction of other new agents expected in mid-2001.

- *Propulsid*<sup>®</sup>. Due to persistent reports of adverse events, Janssen Pharmaceutica withdrew Propulsid, its drug for treatment of gastroesophageal reflux disease. Patients formerly treated with Propulsid will likely switch to similarly priced gastrointestinal drugs, such as proton pump inhibitors or H2 antagonists.

The product was removed from the market four months following the announcement, allowing patients time to contact their health care professionals to discuss alternate treatment options. Patients who meet specific criteria can enroll in a manufacturer-sponsored Propulsid limited distribution program.

Plan sponsor drug expense within the GI drug class is not expected to change significantly due to this withdrawal because patients will change to other similarly priced products.

- *Rezulin*<sup>®</sup>. Former users of Rezulin, an anti-diabetic drug voluntarily withdrawn by Parke-Davis/Warner-Lambert following reports of severe liver damage, will likely switch to Avandia or Actos, products with comparable costs and less risk.
- *Phenylpropanolamine*. In November of 2000, the FDA issued a Public Health Advisory on phenylpropanolamine following a report of its potential to cause hemorrhagic stroke in women. Because this drug was used primarily an over-the-counter cough, cold and diet products, its removal should not affect prescription spend; however, plans will undoubtedly re-evaluate coverage of prescriptions containing phenylpropanolamine and seek alternative therapies.

This advisory resulted from a report from the Yale University School of Medicine that demonstrated an association between the use of phenylpropanolamine and hemorrhagic stroke in women.

### ***The PBM Industry Responds to Rising Costs and Utilization With New Solutions.***

#### **The Three-Tier Benefit Structure Grows in Popularity.**

In 1998, only 36 percent of plans had adopted three-tier copay plan structures. By the spring of 2000, the number of plans offering a three-tier option had grown to 80 percent.

The reason? Unlike a closed formulary, a three-tier plan preserves choice for members. At the same time, it provides cost-management for sponsors. Members pay the lowest copayment for generic drugs, a somewhat higher copayment for formulary brand medications, and the highest copayment for nonformulary brand medications.

Express Scripts studies show that a three-tier structure can significantly lower plan expenditures by shifting a greater portion of cost to members. Further, comparison of two-tier and three-tier plans shows no substantial difference in medical costs.

Three-tier plan enrollees were no more likely than two-tier enrollees to use office visits or hospital services. Children of three-tier plan enrollees were equally likely to fill prescriptions for antibiotics following office visits for otitis media (middle ear infections).

Plans adopting a three-tier structure need to consider a number of factors, including copay amounts for each of the three tiers, market share of preferred drugs and which drugs to assign to the third tier.

### ***The Human Genome is Mapped...and the Door Opened to a New Chapter in Drug Development.***

**The Blueprint of the Human Genome, Completed in 2000, Will Enable Researchers to Target Proteins Responsible for a Host of Genetic Diseases.**

The rough map of the Human Genome, completed ahead of schedule in the summer of 2000, marked a giant step toward development of drugs to combat such diseases as breast cancer, hereditary deafness and skeletal disorders, hemorrhagic strokes, kidney disorders and one type of diabetes.

The human genome project was originally conceived in the mid-1980s. The Department of Energy and the National Institutes of Health were the main research agencies within the US government responsible for the development and planning of the project.

Over the next three to five years, as researchers locate the exact position of all 100,000 genes on human chromosomes and sequence all three billion base pairs, drugs targeted to specific conditions with pinpoint accuracy will begin to emerge. Ultimately, custom drugs matched to an individual's unique genetic profile will be possible.

Eventually, research may enable scientists to predict who will respond most effectively to a particular drug therapy, who may suffer a side effect, as well as designer drugs targeted to each individual and engineered in a much more precise way than today's drugs. This information may also be used to determine an individual's susceptibility to common disorders, allowing the design of programs of effective, individualized preventive medicine focused on lifestyle changes.

We are looking at nothing less than a new era in healthcare, one that promises incalculable potential to eradicate diseases and improve quality and length of life. We cannot predict with certainty when this promise will be fulfilled or how it may eventually impact pharmacy benefit plans. What we can predict is that a new generation of biotech drugs is in our future, and both the rewards and the costs will likely be high.