



EXPRESS SCRIPTS®



top

developments

● from the 2006
Pharmaceutical Landscape

Spring 2007

Dear Friends of Express Scripts,

Ours is a dynamic industry. Every year we see environmental changes that directly affect the prescription-drug benefit. Some of these changes are one-time hits; others have ripple effects whose ultimate effect will not be known for years to come.

The past twelve months were certainly no exception. The landmark Medicare Part D legislation kicked off a year with many changes. We saw the continuance of the silver lining effect of the “me-too” drugs from the early nineties as a number of blockbuster drugs lost their patent and generics were introduced. The phenomenon helped lift many of our plan sponsors to a generic fill rate within the mid-fifties and contributed in part to the lowest overall trends we have seen in a decade. For many plan sponsors, concerns about specialty spend are taking center stage. We also witnessed greater questions about the use of Average Wholesale Price as the industry’s pricing benchmark. And in the 4th quarter of 2006 our industry saw the introduction of a limited list of \$4 generics from some leading retail chains as well as competition in the marketplace for a leading PBM.

We invite you to pause with us and take a look back at the developments that significantly changed the world of pharmaceuticals. What follows is our perspective on these events. We hope you find it informative.

- FDA Activity
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Sincerely,



George Paz

Chairman and CEO

FDA Activity

In our 2005 year-in-perspective report, we anticipated that concerns about the safety of newly approved pharmaceuticals would have a significant effect on FDA activity during 2006. Safety and efficacy concerns halted development of several new drugs previously thought to have the potential for significant contributions to disease treatment. For example, safety concerns halted development of the Dual-PPAR agonists (Pargluva™ and Galida™) for diabetes and a non-narcotic agent for ADHD (Sparlon™). Three other drugs, for complications of diabetes, osteoporosis and sleep, are significantly delayed or may never come to market due to concerns about efficacy. A more insidious indicator of caution is the number of drugs given an “approvable” status on or near their expected approval dates. A total of sixteen drugs were given that status, with the FDA requesting additional data prior to full approval.

Despite these challenges, through the end of November 2006, FDA already exceeded the number of new drugs approved in 2005. Seventeen new molecular entities and four New Biologic License Applications were cleared by FDA, compared to the 2005 total of 20 new drug approvals. Some notable approvals during the course of the year include:

Diabetes Market

Merck's **Januvia™** (sitagliptin) is the first in a new, potential-blockbuster class of medications, known as dipeptidyl peptidase-4 (DPP-4) inhibitors, for the treatment of type 2 diabetes. This once-daily oral medication is approved for use alone or as an add-on therapy to either metformin or thiazolideniones (TZDs). DPP-4 inhibitors work by blocking the body's enzyme responsible for breaking down the gut hormones — glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptides (GIP) — both of which play an important role in maintaining blood glucose control. Interestingly, DPP-4 inhibitors only exhibit their effect when blood sugar is elevated, which results in a low incidence of hypoglycemia (decreased blood sugars). Other DPP-4 inhibitors in later stages of development include Novartis' **Galvus®** (vildagliptin), Bristol-Myers Squibb's saxagliptin and Takeda's SYR-322.

Pfizer, in partnership with Nektar, received final approval for **Exubera®** (insulin [rDNA origin]) inhalation powder for the treatment of adult patients with type 1 and type 2 diabetes. The rapid-acting insulin is inhaled immediately prior to meals using the handheld Exubera inhaler. Patients with type 2 diabetes can use Exubera alone or in combination with oral diabetes medications or longer-acting insulin. Exubera should be used in combination with longer-acting insulin in patients with type 1 diabetes. Exubera is contraindicated in patients with unstable lung disease and in patients who smoke or who have stopped smoking less than six months prior to initiating treatment. Patients are required to have their lung function tested before starting Exubera and periodically thereafter.

Smoking Cessation

Pfizer's **Chantix™** (varenicline) received FDA approval to help smokers stop smoking. Chantix is a nicotine partial agonist that helps decrease the severity of smokers' cravings by providing some nicotine effects, and also blocks the effects of nicotine from cigarettes if they resume smoking. FDA granted this product a priority review because of its “significant potential benefit” to public health. Chantix competes with Zyban® (bupropion, sustained release – GlaxoSmithKline/generics), another non-nicotine therapy for smoking cessation. According to the Centers for Disease Control and Prevention (CDC), an estimated 44.5 million U.S. adults smoke cigarettes. Of these, more than 8.6 million have at least one serious illness caused by smoking.

Generics Update

In 2006, several significant generics became available for the first time, totaling more than \$12 billion in annual sales potential. Generics to Bristol-Myers Squibb's **Pravachol**[®] (pravastatin) and Merck's **Zocor**[®] (simvastatin) top the list. These drugs belong to the cholesterol-reducing class of medications known as HMG-CoA reductase inhibitors, or "statins." Express Scripts worked with its plan sponsors in 2006 to initiate a major formulary change designed to take advantage of these generic introductions. The initiative met with great success. For the statin class, we started the year at a generic-fill rate of just over 8%. With aggressive formulary changes, plus utilization-management programs to complement the changes, we have achieved unprecedented success in preserving and even expanding the market share of products which lost patent protection. By the end of the year, our generic-fill rate for statins stood at 40%.

Although the patent for Pfizer's **Zoloft**[®] (sertraline) expired at the end of June, the first generic was launched in mid-August. Following the market entrance of Teva's generic, Pfizer launched an "authorized" generic through their Greenstone generic unit. Additional generics may be delayed beyond Teva's 180 days of generic exclusivity due to an active patent listed in FDA's Orange Book. Annual U.S. sales of Zoloft are approximately \$3 billion, with a per-member-per-year (PMPY) cost of \$11.67.

GlaxoSmithKline's market-leading nasal steroid **Flonase**[®] (fluticasone propionate nasal spray) experienced first-time generic competition during the first half of 2006. Flonase is used to treat nasal symptoms of seasonal and chronic allergic and nonallergic rhinitis. Annual U.S. sales for Flonase reached nearly \$1 billion with a PMPY cost of approximately \$5.20.

In July 2006, FDA approved multiple generics to Boehringer-Ingelheim's **Mobic**[®] (meloxicam), a product indicated for the relief of arthritis symptoms. Mobic belongs to a class of medications known as non-steroidal anti-inflammatory drugs (NSAIDs), which includes the cyclo-oxygenase-2 (COX-2) inhibitors. Mobic's market share significantly increased following public awareness of safety concerns about the use of the COX-2 inhibitors and market removal of Vioxx[®] (rofecoxib – Merck) and Bextra[®] (valdecoxib – Pfizer). In 2005, annual U.S. sales for Mobic reached approximately \$1.2 billion, and the PMPY cost of Mobic was \$3.89.

Other significant branded medications that experienced generic competition for the first time in 2006 include **Ditropan XL**[®] (oxybutynin e.r. – Johnson & Johnson), **Proscar**[®] (finasteride – Merck), **Zithromax**[®] suspension (azithromycin – Pfizer), and **Actiq**[®] (fentanyl – Cephalon).

Generics to Brand

We also experienced something new during the year — the phenomenon of drugs going from generic back to branded status. This movement was fueled by legal action as well as compliance with new environmental standards set by the Montreal Protocol.

In 2006, Apotex launched an AB-rated generic to Bristol-Myers Squibb's anti-clotting drug **Plavix**[®] (clopidogrel). However, patent litigation is ongoing. When current supplies of the generic are exhausted, additional generic supplies may not become available until the patent expires in 2012. The annual brand sales of Plavix in the U.S. reached approximately \$2.5 billion in 2006, and, based on 2005 Express Scripts Drug Trend Report data, the PMPY cost of Plavix was \$11.40.

Generics to Purdue's **OxyContin**[®] (oxycodone e.r.) have been available since at least mid-2005. However, recent patent litigation settlements may lead to the removal of generics from the market and the re-establishment of a brand-only OxyContin market. Generic OxyContin from Endo has already been taken off the market and the one from Teva will no longer be available in early to mid 2007. Litigation with IMPAX is ongoing, and the future availability of their generic is not known. The authorized generic will likely remain on the market while generic supplies are available.

To comply with the Montreal Protocol for the worldwide removal of ozone-damaging chlorofluorocarbons (CFCs), FDA has established a phase-out date of Dec. 31, 2008, to discontinue sales of albuterol inhalers that use CFCs as a propellant. Currently, all available generic albuterol inhalers use CFCs as propellants, which will ensure their removal from the market. Although the official phase-out will occur at the end of 2008, supplies of generic albuterol inhalers will diminish in 2007. In 2006, two main suppliers of generic albuterol inhalers (IVAX and Warrick) announced plans to discontinue marketing CFC products.

The remaining albuterol inhalers will use an ozone-friendly hydrofluoroalkane (HFA) propellant. Once the transition is complete, the brand-only market will include ProAir[®] (IVAX), Proventil[®] HFA (Schering-Plough) and Ventolin[®] HFA (GlaxoSmithKline). Xopenex[®] HFA (levalbuterol — Sepracor), another albuterol-like product, will also be available. Express Scripts formularies will contain an HFA-containing albuterol inhaler to assure access in the event of a generic albuterol inhaler shortage.

Pandemic Influenza

Through the first ten months of 2006, the World Health Organization documented 258 human avian influenza cases, with 154 deaths due to the disease. Late in 2005, investigators determined that the 1918 Spanish Flu epidemic was caused by an avian influenza very similar to the current H5N1 strain. Over one year later, we continue to wait for a determination of the actual threat caused by avian flu.

Despite the continued reports of birds, in both wild and domestic populations, contracting influenza, bird-to-human transmission thankfully continues to be relatively difficult. More importantly, human-to-human transmission continues to be extremely unlikely.

One could argue that never in the course of disease-preparedness activities has so much energy been committed to preparing for the next pandemic — presumably one caused by the avian influenza virus. Yes, sometime in the future there will likely be a pandemic. In the meantime, continuing to take prudent precautions against contracting the flu, including getting annual flu shots, is advised. In addition, we should all have policies in place to maintain vital business functions in the event of an outbreak.



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Pricing Source Challenged

A 2002 increase in First Data Bank's (FDB) Average Wholesale Price (AWP) for certain drugs led to a class action suit. AWP has been widely used as a benchmark for establishing pricing for most brand drugs and certain generic drugs.

As part of a tentative legal settlement, FDB has agreed to reduce its reported AWP on more than 8,500 drugs by four percent. FDB has also agreed that, two years after the settlement is final, it will stop publishing AWP.

Prior to these legal challenges, the marketplace had already begun to move away from AWP as a widely accepted pricing benchmark. Ideally, a new pricing index that is credible, stable and widely accepted will be phased in over several years to prevent harmful disruption of the marketplace.

\$4 Generic Drug Programs

A major discount retailer's announcement of plans to offer \$4 generic-drug prescriptions garnered media attention, and a few retail pharmacies followed suit.

The discount retailer's program offers a 30-day supply of some commonly prescribed generic medications. Although the list is weighted toward acute conditions, it also includes medications used to treat chronic conditions such as diabetes, high cholesterol and high blood pressure. The \$4 price is available to patients with or without insurance, but the patient is required to pick up the medications in the pharmacy; the price is not available via mail delivery.

The media attention following the announcement focused on the impact to PBMs and other retail pharmacies. Although it is too soon to conclude how this generic program will impact others, the spotlight on generics is good for everyone. When more people ask their doctors about generic alternatives, more doctors are likely to consider generics for all of their patients — a big plus for anyone, such as Express Scripts, working to drive down the cost of prescription drugs.

A more cost-effective savings tool is Home Delivery, which is the safest and most effective way to get medications to patients. The 24/7 service is convenient, confidential and customer-friendly.

Shifting PBM Landscape

The fourth quarter of 2006 saw two major announcements: (1) the proposed merger of Caremark with CVS and (2) the subsequent offer from Express Scripts to purchase Caremark. Although ultimate resolution regarding these announcements is as yet undetermined, the implications for the PBM industry are profound. We believe an independently owned PBM's singular focus on making prescription drugs safer and more affordable is in plan sponsors' best interests. We look forward to creating the world's preeminent pharmacy benefit management company — one that is completely aligned with the goals and interests of our plan sponsors.

Consumer Directed Healthcare

New Health Savings Account Legislation

Passed by Congress and signed into law by President Bush on Dec. 20, 2006, the Tax Relief and Health Care Act of 2006 includes several provisions that will make Health Savings Accounts (HSAs) more attractive. Generally speaking, the law increases the amount people can contribute to HSAs and makes it easier to roll over funds into HSAs from existing tax-advantaged accounts. This should increase employers' interest in offering HSA-qualified, high-deductible health plans (HDHPs) and increase employee enrollment in those plans, once offered.

Express Scripts is well positioned to assist clients who are interested in offering these plans. We provide services, tools, and programs which make administration of HDHPs and HSAs entirely plan sponsor- and member-friendly. Our systems jointly track medical and prescription-drug dollars. We integrate with more than 50 medical administrators. Our Web tools immediately reflect integrated deductible and out-of-pocket totals. Finally, with ChoiceMatters, a comprehensive communication package, members in account-based plans can maximize both financial and health outcomes.

Enrollment in HSA-qualified HDHPs triples from 2005 to 2006

HSA-qualified HDHPs have grown in popularity since President Bush signed HSAs into law in 2003. In March 2005, roughly one million individuals were enrolled in a HSA-qualified HDHP. That amount has since tripled with approximately three million individuals enrolled as of January 2006. Enrollment is expected to increase through 2007.

Within our own book of business we have seen substantial increases in the number of plan sponsors offering account-based plans to their beneficiaries.