NEW DRUG APPROVALS

**Viberzi for IBS**

Eluxadoline (Viberzi, Patheon Pharmaceuticals/Forest Pharmaceuticals) has secured FDA approval to treat adults who have irritable bowel syndrome with diarrhea (IBS-D), which is characterized mainly by loose or watery stools at least 25% of the time.

Eluxadoline, taken orally twice daily with food, activates receptors in the nervous system that can lessen bowel contractions. Its safety and efficacy for the treatment of IBS-D were established in two double-blind, placebo-controlled clinical trials in which 2,425 patients were randomly assigned to receive eluxadoline or placebo. Eluxadoline was more effective than placebo in simultaneously reducing abdominal pain and improving stool consistency during 26 weeks of treatment.

The most common adverse events with eluxadoline included constipation, nausea, and abdominal pain. The most serious known risk associated with the medication is the risk of spasm in the sphincter of Oddi, the smooth muscle that surrounds the end portion of the common bile and pancreatic ducts, which can result in pancreatitis. Eluxadoline should not be used in patients with a history of bile-duct obstruction, pancreatitis, severe liver impairment, or severe constipation, and in patients who drink more than three alcoholic beverages a day.

Source: FDA, May 27, 2015

**Stiolto Respimat for COPD**

The FDA has approved tiotropium bromide/olodaterol inhalation spray (Stiolto, Boehringer Ingelheim [BI]) for long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis, emphysema, or both. The medication, delivered via the propellant-free Respimat inhaler, is not indicated for the treatment of asthma or acute deterioration of COPD.

Tiotropium, a long-acting anticholinergic, is the active ingredient in BI’s Spiriva Respimat and Spiriva HandiHaler. Olodaterol, BI’s Striverdi Respimat, is a long-acting beta2 agonist that was designed to complement the efficacy of Spiriva. Olodaterol has a rapid onset of action that results in improved airflow five minutes after the first dose.

The FDA’s approval of Stiolto Respimat was based on the pivotal phase 3 TONADO 1 and 2 trials in more than 5,000 COPD patients. The results showed that tiotropium/olodaterol Respimat provided statistically significant improvements in lung function compared with tiotropium or olodaterol alone. Tiotropium/olodaterol Respimat more than doubled the improvement in lung function compared with tiotropium Respimat in patients who had no prior maintenance bronchodilator therapy at baseline (148 mL versus 72 mL, respectively). Tiotropium/olodaterol Respimat significantly improved lung function compared with tiotropium Respimat in patients across all COPD stages, with the greatest improvements in early COPD.

The TONADO trials showed that Stiolto Respimat has a safety profile similar to that of tiotropium or olodaterol alone.

Sources: Boehringer Ingelheim, May 26, 2015, and May 20, 2015

**Generic Approvals**

**Risedronate Sodium Tablets**

Teva Pharmaceutical Industries Ltd. has launched the first U.S. generic risedronate sodium 5-mg, 30-mg, and 35-mg tablets, equivalent to Actonel (Actavis). Used to treat or prevent osteoporosis in women after menopause, risedronate sodium tablets help increase bone mass and help reduce the chances of having a spinal or nonspinal fracture. Risedronate sodium tablets are also used to treat or prevent osteoporosis in men or women who are taking corticosteroid medica-

tions and to treat Paget’s disease of the bone. Actonel had U.S. sales of approximately $157 million in 2014, according to IMS data.

Source: Teva Pharmaceutical Industries Ltd., June 1, 2015

**Alosetron Hydrochloride Tablets**

The FDA has approved the sale of 0.5-mg and 1-mg alosetron hydrochloride tablets by Roxane Laboratories, Inc., the first generic versions of Lotronex (Prometheus Laboratories, Inc.). Alosetron is a selective serotonin 5-HT3 antagonist indicated for women with severe, chronic, diarrhea-predominant irritable bowel syndrome who have had anatomical or biochemical abnormalities of the gastrointestinal (GI) tract excluded and have not responded adequately to conventional therapy.

Alosetron has a boxed warning for infrequent but serious GI adverse reactions, including ischemic colitis and serious complications of constipation. It is subject to a risk evaluation and mitigation strategy.

Sources: FDA, May 4, 2015, and Lotronex prescribing information

**Eptifibatide**

Teva Pharmaceutical Industries Ltd. has received FDA approval to market eptifibatide 75 mg/100 mL, the first generic version of Integrilin (Merck). Eptifibatide is a platelet aggregation inhibitor indicated for treatment of acute coronary syndrome and treatment of patients undergoing percutaneous coronary intervention (including intracoronary stenting).

Sources: FDA, June 5, 2015, and Integrilin prescribing information

**NEW INDICATIONS**

**Xifaxan for IBS**

Rifaximin (Xifaxan, Salix Pharmaceuticals) has won FDA approval for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.
Rifaximin is taken orally three times a day for 14 days for the treatment of abdominal pain and diarrhea in patients with IBS-D, which is marked by loose or watery stools at least 25% of the time. Patients who experience a recurrence of symptoms can receive an additional 14-day treatment course up to two times.

Rifaximin, an antibiotic derived from rifampin, was previously approved to treat travelers’ diarrhea caused by *Escherichia coli* and to reduce the risk of recurring overt hepatic encephalopathy in adults. Rifaximin’s exact mechanism of action in the treatment of IBS-D is not known but is thought to relate to changes in the bacterial content of the gastrointestinal tract.

The safety and efficacy of rifaximin for IBS-D treatment were established in three double-blind, placebo-controlled trials. In the first two studies, 1,258 patients were randomly assigned to receive rifaximin or placebo for 14 days and were then followed for a 10-week treatment-free period. More patients treated with rifaximin than with placebo reported improvements in abdominal pain and stool consistency.

A third trial evaluated repeat courses of rifaximin because patients with IBS-D can develop recurrent signs and symptoms after a single treatment course of the drug. A total of 636 patients with disease recurrence were randomly assigned to receive either rifaximin or placebo for two additional 14-day courses separated by 10 weeks. More patients treated with rifaximin than with placebo were responders in abdominal pain and stool consistency in this phase of the study.

The most common adverse events in patients treated with rifaximin for IBS-D include nausea and increased levels of alanine aminotransferase. If the patient’s diarrhea does not improve or worsens after treatment with rifaximin, the clinician should check for *Clostridium difficile* enterocolitis. Caution should be used when administering rifaximin in patients with severe liver impairment or in combination with certain other drugs.

Source: FDA, May 27, 2015

**Meropenem for Infant Abdominal Infections**

The antibiotic meropenem (Merrem, AstraZeneca, and generics) is now FDA-approved to treat abdominal infections in children younger than 3 months of age.

A study by a National Institutes of Health (NIH) research network evaluated the drug for treating complicated intra-abdominal infections (cIAIs) in this age group. Among preterm infants, intestinal perforation or leakage (part of cIAIs) can be life-threatening. The study was conducted under the Best Pharmaceuticals for Children Act, which directs the NIH to study drugs used in children but not previously tested in children or in specific pediatric age groups.

Meropenem, a broad-spectrum antibiotic, is effective against a wide variety of bacteria. It has been approved to treat cIAIs and complicated skin infections in adults and older children and to treat children 3 months of age and older with bacterial meningitis.

Several years ago, physicians began to prescribe meropenem for preterm infants with serious abdominal infections, an unapproved use. The FDA requested the NIH study to evaluate meropenem’s dosing and safety for treating cIAIs in this population. Doctors now have dosing guidelines for premature infants in various age groups.

Physicians often extrapolate from studies of adults when prescribing for pediatric patients because many drugs have never been tested specifically in children. However, because of their smaller size, differences in metabolism, and other physical differences from adults, children respond differently to many drugs.

Source: NIH, May 29, 2015

**Sirolimus for Lymphangioleiomyomatosis**

Sirolimus (Rapamune, Wyeth Pharmaceuticals) has become the first FDA-approved drug for the treatment of lymphangioleiomyomatosis (LAM), a very rare progressive lung disease that primarily affects women of childbearing age.

LAM is characterized by an abnormal growth of smooth-muscle cells that invade lung tissues as well as blood and lymph vessels, obstructing airflow and impeding oxygen delivery. Sirolimus, available as a tablet and an oral solution, was approved in 1999 as an immunosuppressive agent to help prevent rejection of transplanted kidneys. Sirolimus received breakthrough therapy, priority review, and orphan drug designations for this indication.

Sirolimus was compared with placebo in 89 LAM patients for a 12-month treatment period, followed by a 12-month observation period. Between the two groups, the difference in the average decrease in the forced expiratory volume in one second during the 12-month treatment period was approximately 153 mL. After sirolimus was discontinued, the decline in lung function resumed at a rate similar to that of the placebo group.

The most common adverse events associated with sirolimus included mouth and lip ulcers, diarrhea, abdominal pain, nausea, sore throat, acne, chest pain, leg swelling, upper respiratory-tract infection, headache, dizziness, muscle pain, and elevated cholesterol levels. Serious adverse events, including hypersensitivity and edema, have been observed in renal transplant patients.

Source: FDA, May 28, 2015

**Promacta for Pediatric Chronic Immune Thrombocytopenia**

The FDA has approved eltrombopag (Promacta, Novartis) for the treatment of children 6 years of age and older with chronic immune thrombocytopenia (ITP) who have had an insufficient response to
corticosteroids, immunoglobulins, or splenectomy. The drug was approved in 2008 for use in adults with the same condition.

Eltrombopag is a once-daily oral thrombopoietin receptor agonist that induces the stimulation and differentiation of megakaryocytes from bone-marrow stem cells to increase platelet production.

The new approval was based on data from two double-blind, placebo-controlled trials. Treatment with eltrombopag significantly increased and sustained platelet counts among some pediatric patients with chronic ITP, and some patients taking concomitant ITP medications were able to reduce or discontinue their use of these treatments, primarily corticosteroids. The most common adverse events in patients 6 years of age and older included upper respiratory-tract infection, nasopharyngitis, and rhinitis.

Sources: Novartis, June 11, 2015, and Promacta prescribing information

**Qudexy XR for Pediatric Seizures**

The FDA has expanded the approved indications for topiramate extended-release capsules (Qudexy XR, Upsher-Smith Laboratories, Inc.) to include initial monotherapy in patients 2 years of age and older who are experiencing partial-onset seizures (POS) or primary generalized tonic-clonic seizures. The capsule contents can be sprinkled onto soft food, a useful option for young children who have difficulty swallowing whole capsules or tablets.

The medication, a once-daily, broad-spectrum antiepileptic, was previously approved for use as initial monotherapy in patients 10 years of age and older with POS or primary generalized tonic-clonic seizures. It is also approved as an adjunctive therapy in patients 2 years of age or older with POS, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome.

Source: Upsher-Smith Laboratories, Inc., June 1, 2015

**NEW FORMULATION Invega Trinza, Used 4 Times A Year for Schizophrenia**

The FDA has approved Invega Trinza (Janssen Pharmaceuticals), a long-acting injectable suspension version of the second-generation antipsychotic paliperidone palmitate that is given once every three months to treat schizophrenia. Before starting Invega Trinza, patients must be treated with the once-monthly form of paliperidone palmitate (Invega Sustenna, Janssen) for at least four months.

A long-term, phase 3 maintenance trial evaluated the efficacy and safety of three-month paliperidone palmitate compared with placebo in delaying the time to relapse of schizophrenia symptoms. This randomized study had four phases: a three-week screening phase; a 17-week, flexible-dose, open-label transition phase; a 12-week, open-label maintenance phase; and an open-ended double-blind phase. A total of 305 patients ages 18 to 70 years of age were randomly assigned to receive three-month paliperidone palmitate (n = 160) or placebo (n = 145) in the double-blind phase.

In an interim analysis, the time to first relapse significantly favored the paliperidone palmitate group compared with the placebo group (hazard ratio, 3.45); the median time to relapse was 274 days for placebo but not estimable for three-month paliperidone palmitate. Of the patients treated with paliperidone palmitate, 93% did not experience a significant return of schizophrenia symptoms.

In the double-blind phase of the study, 183 patients (62% with paliperidone palmitate, 58% with placebo) had at least one treatment-emergent adverse event. Those noted more frequently in the group receiving paliperidone palmitate included headache, weight gain, nasopharyngitis, and akathisia.

Sources: Janssen Pharmaceuticals, May 19, 2015; Invega Trinza prescribing information; and JAMA Psychiatry, March 29, 2015

**DRUG NEWS Breakthrough Therapies Rindopepimut for Glioblastoma**

Rindopepimut (Rintega, Celldex Therapeutics, Inc.) has received an FDA breakthrough therapy designation for the treatment of adults with epidermal growth factor receptor variant III (EGFRvIII)--positive glioblastoma (GB).

Updated results from a randomized, double-blind, phase 2 study of rindopepimut in patients with EGFRvIII-positive recurrent GB were reported at the 2015 American Society of Clinical Oncology annual meeting in Chicago. The ReACT trial was designed to determine whether adding rindopepimut to standard-of-care bevacizumab (BV; Avastin, Genentech) would improve patient outcomes. A total of 140 patients (intent to treat [ITT], n = 73; per protocol [PP], n = 67) were bevacizumab-naïve at study entry.

For rindopepimut plus BV compared with control plus BV, progression-free survival at six months was 36% versus 16% in the ITT group and 30% versus 12% in the PP group, respectively. At 12 months, 45% of rindopepimut patients (ITT) were alive compared with 31% of control patients. The corresponding survival rates at 18 months were 30% and 15%.

And for rindopepimut plus BV compared with control plus BV, objective responses were confirmed in 30% versus 18% of ITT patients and in 31% versus 16% of PP patients. Five patients in the rindopepimut arm experienced durable responses (DRs) of more than six months, three of which exceeded 12 months. Only one PP patient in the control arm experienced a DR longer than six months; none exceeded 12 months.

Rindopepimut is an investigational EGFRvIII-specific therapeutic vaccine.
EGFRvIII is expressed in tumors in approximately 30% of GB patients, who typically fare worse than the overall GB population. The most common adverse events associated with rindopepimut include injection-site reactions, fatigue, rash, nausea, and pruritus.

Source: Celldex Therapeutics, May 31, 2015

**Actemra for Systemic Sclerosis**

The FDA has designated tocilizumab (Actemra, Roche) a breakthrough therapy for systemic sclerosis, a rare, chronic disorder also known as scleroderma that is characterized by blood vessel abnormalities and degenerative changes and scarring in the skin, joints, and internal organs.

The designation was granted based on data from the phase 2 faSScinate study. While the primary endpoint of improvement in skin thickening at 24 weeks was not met, a meaningful trend was observed, and there was continued improvement in skin thickening between weeks 24 and 48. The extent and severity of skin thickness correlates to disease worsening, increased disability, and decreased survival. Roche has now initiated a global phase 3 study.

Tocilizumab is an anti-interleukin-6 receptor biologic approved for the treatment of adults with moderate-to-severe active rheumatoid arthritis and other rheumatic ailments.

Source: Roche, June 10, 2015

**Olipudase Alfa for Niemann–Pick Type B**

The FDA has granted breakthrough therapy status to the enzyme-replacement treatment olipudase alfa (Genzyme/Sanofi), which is being investigated for use in patients with nonneurological manifestations of acid sphingomyelinase deficiency (ASMD), also known as Niemann–Pick disease type B.

ASMD is a life-threatening disorder caused by insufficient activity of the ASM enzyme that results in toxic accumulation of sphingomyelin. Supplemetting the defective or deficient native enzyme with olipudase alfa allows the breakdown of sphingomyelin. A phase 1b study supported olipudase alfa’s continued development for use in nonneurological manifestations of ASMD. Genzyme has started enrollment in a phase 1/2 pediatric study and is preparing a phase 2/3 study in adults.

Niemann–Pick types A and B are caused by the same enzymatic deficiency, but type A is characterized by neurological involvement.

Source: Genzyme, June 4, 2015

**Daclatasvir/Sofosbuvir for HCV**

The FDA has amended a previously granted breakthrough therapy designation for Bristol-Myers Squibb’s daclatasvir/sofosbuvir combination to focus on hepatitis C (HCV) genotype 1 patients who have advanced cirrhosis or who develop recurrent genotype 1 HCV after a liver transplant.

The designation is supported by data from ALLY-1, a phase 3 clinical trial evaluating a 12-week, once-daily regimen of daclatasvir/sofosbuvir with ribavirin for the treatment of this challenging HCV patient population.

Daclatasvir is an NSSA complex inhibitor being investigated in multiple treatment regimens and patient populations. The FDA granted a breakthrough therapy designation for the combination of daclatasvir and sofosbuvir (Sovaldi, Gilead Sciences) in 2014, but significant developments have transformed HCV therapy since then. The ALLY program was established to study the daclatasvir/sofosbuvir combination in HCV populations with high unmet needs.

Source: Bristol-Myers Squibb, May 20, 2015

**Fast-Track Designations**

**Evofosfamide for Pancreatic Cancer**

EMD Serono has received an FDA fast-track designation for the development of evofosfamide (TH-302), administered in combination with gemcitabine, as therapy for previously untreated patients with metastatic or locally advanced unresectable pancreatic cancer.

Evofosfamide is thought to be activated under severe tumor hypoxic conditions, a feature of many solid tumors. The compound, currently in phase 3 trials, is being developed in collaboration with Threshold Pharmaceuticals, Inc.

Evofosfamide previously received a fast-track designation for development in combination with doxorubicin for the treatment of advanced soft tissue sarcoma.

Source: EMD Serono, May 12, 2015

**Luspatercept for Beta-Thalassemia**

The FDA has granted fast-track designations to luspatercept (Celgene Corporation/ Acceleron Pharma Inc.) for two indications: treatment of transfusion-dependent beta-thalassemia and treatment of non–transfusion-dependent beta-thalassemia. The companies expect to start a phase 3 clinical program in 2015.

Luspatercept is a modified activin receptor type IIB fusion protein that acts as a ligand trap for members of the transforming growth factor-beta superfamily involved in the late stages of red blood-cell production. Luspatercept is in phase 2 clinical trials in patients with beta-thalassemia and in patients with myelodysplastic syndromes.

Source: Celgene Corporation/Acceleron Pharma Inc., May 18, 2015

**Zerbaxa Dose Labeling Altered**

The FDA is warning health care professionals about the risk for dosing errors with the antibacterial drug ceftolozane/tazobactam (Zerbaxa, Cubist Pharmaceuticals).
Ketoacidosis Reported With SGLT2 Inhibitors

Use of sodium-glucose cotransporter-2 (SGLT2) inhibitors to treat type-2 diabetes may lead to ketoacidosis, says the FDA, which is considering whether changes are needed in the medications’ prescribing information.

The FDA advised health care professionals to evaluate for the presence of acidosis in patients experiencing difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Providers should discontinue SGLT2 inhibitors if acidosis is confirmed and should take appropriate measures to correct the acidosis and monitor sugar levels.

SGLT2 inhibitors cause the kidneys to remove sugar from the body through the urine. Their safety and efficacy have not been established in patients with type-1 diabetes, and the FDA has not approved them for use in these patients.

A search of the FDA Adverse Event Reporting System (FAERS) identified 20 cases of acidosis reported as diabetic ketoacidosis (DKA), ketoacidosis, or ketoacidosis in patients treated with SGLT2 inhibitors from March 2013 to June 6, 2014. All patients required emergency department visits or hospitalization to treat the ketoacidosis. Since June 2014, the FDA has received additional FAERS reports.

DKA usually develops when insulin levels are too low or during prolonged fasting. It is most common in type-1 diabetes patients and usually accompanies high blood sugar levels. The FAERS cases were atypical for DKA because most of the patients had type-2 diabetes and their blood sugar levels, when reported, were only slightly increased compared to typical DKA cases. Factors identified in some reports as potential ketoacidosis triggers included major illness, reduced food and fluid intake, and reduced insulin dose.

SGLT2 inhibitors and combination products include canagliflozin (Invokana, Janssen); canagliflozin/metformin (Invokamet, Janssen); dapagliflozin (Farxiga, AstraZeneca); dapagliflozin/metformin extended-release (Xigduo XR, AstraZeneca); empagliflozin (Jardiance, Boehringer Ingelheim); and empagliflozin/linaclotide (Glyxambi, Boehringer Ingelheim).

Source: FDA, May 15, 2015

Antibiotic-Resistant Shigellosis

The Centers for Disease Control and Prevention (CDC) is receiving reports of infections with Shigella strains that are not susceptible to ciprofloxacin or azithromycin, the antimicrobial agents most commonly used to treat shigellosis.

Some Shigella was resistant to ampicillin, ciprofloxacin, nalidixic acid, streptomycin, sulfisoxazole, tetracycline, and trimethoprim/sulphamethoxazole; had azithromycin minimum inhibitory concentration of greater than 16 mcg/mL; and harbored macrolide resistance genes mphA and ermB.

Most cases have been reported among men who have sex with men in Illinois, Minnesota, and Montana and among international travelers, but cases are also occurring among other populations. Shigellosis is very contagious and can spread quickly through communities and across different populations, the CDC says.

The CDC encourages clinicians to obtain stool cultures from patients suspected of having shigellosis and to base treatment for shigellosis, when needed, on the antimicrobial susceptibility profile of the individual isolate or, during a local outbreak, the profile of the outbreak strain. Shigellosis patients should be counseled about the importance of meticulous hand washing after using the toilet and avoiding activities most likely to transmit the infection to others, such as preparing food for others, swimming, group play among young children, and certain sexual activities.

Source: CDC, June 4, 2015

Medication Recalls

More Mylan Injectable Products

Mylan Institutional has added seven lots of gemcitabine and one lot of methotrexate to a previously announced recall of injectable products because foreign particulate matter was found during sample testing. Like the previously recalled
eight lots of medications, the latest lots—distributed in the U.S. between January 8, 2014, and February 10, 2015—were packaged by Agila Onco Therapies Ltd., a Mylan subsidiary. Some have Pfizer Injectable labels. A list of the new lots is available at http://tinyurl.com/MylanInjectablesRecall2. Consumers with questions can contact Mylan Customer Relations at 1-800-796-9526, Monday through Friday, 8 A.M. to 5 P.M. Eastern time.

Source: Mylan, June 8, 2015

RESEARCH BRIEFS

Study: Antibiotic Use Could Be Halved in Abdominal Infections

The duration of antibiotic treatment for complicated abdominal infections can be cut in half and stay just as effective, researchers at 23 institutions in the U.S. and Canada have determined. The finding could help prevent the development of antibiotic-resistant “superbugs.”

The researchers, led by a team at the University of Virginia (UVA) School of Medicine, looked at the treatment of infections after the source of the infection was addressed, such as the removal of an inflamed appendix. They found that administering antibiotics for four days was as effective as treatments spanning eight days.

It is crucial that doctors have reliable information for providing treatment that is both effective and conservative in its antibiotic use, the authors said. Doctors traditionally have given antibiotics until all symptoms disappear—typically a week or two. More recent guidelines have called for courses of four to seven days, but many doctors have resisted the change and have continued to administer antibiotics for much longer.

The Study to Optimize Peritoneal Infection Therapy (STOP-IT) looked at 517 patients in the U.S. and Canada who had an abdominal infection. After the sources of the infections were addressed, half were given antibiotics until two days after the resolution of fever, leukocytosis, and ileus, while the other half were given antibiotics for only four days.

The outcomes were similar between groups. Surgical-site infection, recurrent intra-abdominal infection, or death occurred in 21.8% (56 of 257) of the experimental group compared with 22.3% (58 of 260) of the control group. The median durations of antibiotic therapy were 4.0 days in the experimental group and 8.0 days in the control group.

Sources: UVA Health System, June 8, 2015, and New England Journal of Medicine, May 21, 2015

Costs Go Up, Up, and Away

A trio of reports in May show that rising health care costs continue to challenge employers and consumers alike, with prescription drugs responsible for a large share of the pressure.

The cost of health care for a typical American family of four covered by an employer-sponsored preferred provider plan will rise 6.3% ($1,456) to $24,671 in 2015, according to the 2015 Milliman Medical Index from consultant Milliman, Inc. The employer will pay $14,198 and the employee, through payroll deductions and cost-sharing at the time of service, will pay $10,473. Of this year’s increase, $467 results from prescription drug costs, which rose 13.6% after a five-year period during which they went up an average of 6.8% a year. Health care costs for this family have doubled in the past decade and tripled since 2001.

A second report, from Kalorama Information, found that Americans’ out-of-pocket spending on health care reached $416 billion in 2014 and will grow 8% a year to $608 billion by 2019. Kalorama expects annual growth of 9.5% on direct expenditures (partly because of the popularity of high-deductible health plans); 9.5% on copays as part of office visits, hospital visits, and drug purchases; and 7.1% on premiums. Prescription medications represent the single largest out-of-pocket health care expenditure for the average person, comprising 43% of the total.

And a third report warns that the prices of generic drugs, which have helped contain Americans’ health care spending, are soaring in some cases. The AARP Public Policy Institute’s Rx Price Watch Report found that retail prices for 280 generic prescription drugs widely used by older Americans fell an average of 4% in 2013—the smallest average annual decline since at least 2006. While 73% of the generic drug products in the study experienced price decreases, 27% had retail price increases, and 11 drugs had retail price increases of more than 30%. The cost of 100-mg doxycycline hyclate tablets and capsules rose more than 1,700%.

Sources: Milliman, May 19, 2015; Kalorama, May 27, 2015; and AARP, May 28, 2015

Osteoporosis Drugs Underused

People who have one hip fracture are at risk for more. Medications such as bisphosphonates can reduce that risk, but many people don’t fill prescriptions for the drugs—regardless of their country’s health care system and despite the availability of effective, safe, and affordable medications.

Researchers who looked at data on 86,202 patients in the U.S., Korea, and Spain found similarly low use of osteoporosis medicines. Only 11% of patients with Medicare and 13% with commercial insurance in the U.S., 39% of patients in Korea, and 25% in Spain had filled one or more prescriptions. The numbers did not rise over time. What’s more, the proportion of U.S. patients who received an osteoporosis medication was lower after the first hip fracture than before it.

Better access to health care or lower copayment requirements did not seem to
Handwritten Prescriptions Flop

A computer crash at Taipei Veterans General Hospital forced old-school prescription writing—and all 114 physicians failed to write a flawless prescription.

Normally, doctors use a computerized prescriber order-entry (CPOE) system that allows them to select drugs by keying in at least three letters and searching a drop-down list. They then need only to verify the default values in an autogenerated prescription. More than 8,000 ambulatory prescriptions are processed daily.

When the computer went down for 3.5 hours, the hospital switched to paper prescription forms. Hospital clinical pharmacists later reviewed the handwritten prescriptions and corresponding medical records, looking for correct patient and prescriber data, such as name, age, and diagnosis, and correct drug data, such as dosage form, dose, route, and frequency. Each prescription was assessed for completeness (all necessary fields were filled in), legibility (no need to reconfirm with prescribers, patients, or medical records), and accuracy (no misspellings, unavailable dosage forms, or similar errors).

While the computer was down, 114 physicians wrote 1,418 prescriptions with 3,805 drug items for 1,369 patients. Not one prescription was filled out completely. The researchers found a mean of 1.6 omitted fields of patient and prescriber data and 9.6 omitted fields of drug data.

Only 64 prescriptions were complete, legible, and accurate in all eight fields of patient and prescriber data; age, diagnosis, and sex were most commonly omitted. The patient’s name and age were the most frequently illegible, while the identification number and patient’s name were the most frequently inaccurate. Only 17 of 3,805 prescribed drug items were complete, legible, and accurate. Dosage form, route, and quantity were the most frequently omitted, while strength, dose, and drug name were the most frequently wrong.

Suggested reasons for the unsatisfactory quality of handwritten prescriptions included lack of time, poor training, or the possibility that the physicians—having used the CPOE system for a while—had simply forgotten how to write prescriptions.

Source: Clinical Therapeutics, May 2015

Pregabalin for Spinal Pain

Pregabalin (Lyrica, Pfizer) improves neuropathic pain and pain-related sleep problems within days for patients with spinal cord injuries, according to a retrospective analysis by University of Miami researchers.

Previously, two large placebo-controlled trials found treatment with pregabalin led to statistically significant improvement in pain and sleep, but the first time-point evaluated was at one week, with weekly scores defined as the average score over the previous seven days. Patients began with 150 mg per day of pregabalin or placebo; doses were adjusted as needed to 600 mg per day in divided doses. In both studies, patients used daily diaries to rate pain and pain-related sleep disturbance.

To quantify the timing of pregabalin’s therapeutic effect, the researchers compared the daily group average of the patients’ scores over the first 14 days in each of the two trials. They defined time to improvement as the first of two consecutive days for which the mean score on the relevant scale was statistically significantly lower for the drug group. They also measured the time required to achieve a greater-than-1-point improvement in the scores of patients with a clinically meaningful and sustained response. Finally, they divided patients into groups according to whether they were receiving concomitant medications.

The studies used for analysis were not designed or powered to study the timing of therapeutic effect. The day-by-day analysis of time to significant pain and sleep relief was based solely on the statistical difference between pregabalin and placebo. However, in both trials, pregabalin made a difference early on. The first significant improvement in pain was seen on day 1 for one trial (−1.15 change from baseline) and day 2 for the other (−0.52 change from baseline). Pain-related sleep interference was significantly improved by day 1 in both studies.

Source: Clinical Therapeutics, May 2015

Glutamine in ICU Hyperglycemia

Intensive care unit (ICU) patients typically have a marked, sustained drop in glutamine as well as digestive dysfunction, and their uninjured tissues donate insulin-mediated glucose to the injured tissues. For those and other reasons, guidelines recommend supplementation with glucose and insulin—but ICU patients are also at risk for insulin resistance and hyperglycemia.
Researchers from Clinical Emergency Hospital of Bucharest compared parenteral glutamine supplementation with Dipeptiven to standard nutritional treatment in an open-label trial of 82 polytrauma patients ages 20 to 60 years, who were randomly assigned to either parenteral Dipeptiven 0.5 g/kg per day or isocaloric isoproteic nutritional support. Supplementation was continued for at least seven days.

After six days, 63% of glutamine-supplement patients had had no hyperglycemic episodes, and 37% required exogenous insulin. By comparison, 51% of the control group required insulin. The highest mean dose of insulin with glutamine supplementation was on day 1 (24 units); the lowest was on day 6 (9 units). The control group required roughly twice as much insulin (44 units on the first day, 18 units on the last day).

The researchers note that the glucose levels in the glutamine-supplemented patients were not significantly lower than in the control patients, but showed more consistency across a narrower range.

Source: Clinical Nutrition, June 2015

Breast Cancer Subtypes Tallied

Data on the U.S. incidence of the four major molecular subtypes of breast cancer is now available by age, race and ethnicity, socioeconomic level, and other factors, according to the National Cancer Institute (NCI) Annual Report to the Nation on the Status of Cancer, 1975–2011.

Beginning in 2010, cancer registries were required to report hormone receptor (HR) status and expression of the HER2 gene for breast cancer cases. This will help researchers stratify breast cancer by risk, the NCI says. The report suggests that some disparities in breast cancer incidence and mortality across racial and ethnic groups are related to differences in the incidence of subtypes.

HR+/HER2− (“triple negative”) breast cancer, which accounts for 10% of cases, although rates were higher in Idaho, Tennessee, and Pennsylvania. Rates of HR−/HER2+ breast cancer, which accounts for 5% of cases, were the lowest for all races and ethnicities, with no statistically significant differences between the national and state rates. Triple-negative rates were lower in the Northwest U.S. and higher in the Southeast.

Over time, the data should help refine treatments and perhaps lead to new ones. The researchers point out that very few effective drugs exist for women with triple-negative breast cancer compared with HR+ or HER2+ cancers.

Source: National Cancer Institute, March 30, 2015

Devices Reusable Only So Long

Reusable medical devices have become more complex, making reproprocessing (cleaning and disinfection) more complex, too. And that may worsen cross-infection. The flexible endoscope, for instance, is vulnerable to contamination: Over its lifetime of use (typically five to 10 years), repetitive reproprocessing can damage the endoscope’s inner and outer surfaces, allowing microorganisms to get a foothold and form a biofilm. Blocking that initial adhesion is the first step to reducing the pathogenesis of foreign-body–related infections, say South Korean researchers.

They assessed the effects of material alterations caused by repetitive use and reproprocessing on the adhesion properties of microorganisms and organic contaminants. They chose a “worst-case scenario” for surface abrasion on the endoscope, based on five uses a day, 233 days a year, for 10 years. Reprocessing was defined as seven wipings a day with gauze (pre-cleaning and manual cleaning), or 81,550 times. Two flexible parts of an endoscope and four insertion parts were mounted in a simulator that accelerated aging. Then, using stereomicroscopy, the researchers compared the parts that had been aged with parts that had not. They tested for residual organic substances (protein, lipid, carbohydrate, hemoglobin) and microorganisms (such as Escherichia coli and Mycobacterium terrae).

The aged endoscope parts, both inner and outer, had more abrasions, holes, dents, and other damage. The researchers also found higher levels of residual organic substances and bacteria on those surfaces. The results suggest that physical alteration is a major factor affecting adhesion of microorganisms, rather than chemical alterations such as those from gastric acid and cleaning agents.

So reusable devices don’t have infinite lifespans, the researchers suggest: It’s better to limit how many times they’re reused.

Source: American Journal of Infection Control, May 2015

Melanoma Doubles in 30 Years

Melanoma rates doubled between 1982 and 2011, but comprehensive skin-cancer prevention programs could prevent 20% of new cases between 2020 and 2030,
according to the Centers for Disease Control and Prevention (CDC).

While the rates of most other cancers are declining, melanoma rates increased from 11.2 cases per 100,000 people in 1982 to 22.7 cases per 100,000 people in 2011. More than 90% of melanoma skin cancers are blamed on skin-cell damage from exposure to ultraviolet radiation.

Melanoma causes more than 9,000 U.S. deaths a year. In 2011, more than 65,000 melanoma skin cancers were diagnosed. But by 2030, effective community skin-cancer prevention programs could prevent an estimated 230,000 melanoma skin cancers and save $2.7 billion in treatment costs. Successful programs feature community efforts that combine education, mass-media campaigns, and policy changes to increase skin protection for children and adults.

Researchers reviewed data from the CDC’s National Program of Cancer Registries and the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program (SEER) to determine melanoma rates.

Source: CDC, June 2, 2015

**DEVICE NEWS**

**Can Hospira Pumps Be ‘Hacked’?**

Security vulnerabilities could allow an unauthorized user to remotely access some Hospira infusion pumps and interfere with their function—potentially causing overdoses or underinfusion of critical therapies, according to the FDA and the Department of Homeland Security (DHS).

The Hospira LifeCare PCA3 and PCA5 Infusion Pump Systems, designed for continuous delivery of drugs, can be programmed remotely through a health care facility’s Ethernet or wireless network. The FDA and DHS say an independent researcher released information about security vulnerabilities—including software codes—that could let an unauthorized user remotely modify the dosage the pumps deliver. Even a poorly skilled attacker could exploit some vulnerabilities, the DHS says.

Hospira argues that while drug libraries, software updates, and pump configurations can be modified, it is not possible to remotely operate the pump; a clinician must be present and manually program a specified dosage.

The DHS Industrial Control Systems Cyber Emergency Response Team (ICS-CERT) has been working with Hospira since May 2014 to address the vulnerabilities. Hospira has developed a new version of the system that it says will mitigate the problems; the FDA is reviewing a premarket 510(k) submission.

The FDA is not aware of any adverse events or unauthorized device access related to these vulnerabilities. Health care facilities can reduce the risk of unauthorized access by implementing recommendations outlined at http://tinyurl.com/HospiraLifeCareAlert.

Sources: FDA and ICS-CERT, May 13, 2015

**FDA Targets Soft-Tissue Fillers**

Rare but serious injuries may occur when soft-tissue fillers are unintentionally injected into facial blood vessels, the FDA warns. Such injections can block blood vessels, restrict blood supply to tissues, and result in embolization if the material travels to other parts of the body—potentially causing vision impairment, blindness, stroke, and necrosis of the skin and underlying facial structures.

An FDA review of literature and adverse event reports identified injection locations where blood-vessel blockages have been reported more often, including the skin between the eyebrows and nose, in and around the nose, the forehead, and around the eyes.

Soft-tissue fillers, also called dermal fillers, injectable facial implants, or wrinkle fillers, can create a smoother or fuller appearance of the face. They are FDA-approved to reduce the appearance of wrinkles or to augment lips or cheeks. Approved indications vary depending on the product; the FDA may not have reviewed their use in some parts of the body. They should be injected only by health care providers who have appropriate training and experience and who are knowledgeable about the anatomy at and around the injection site.

The FDA is working with manufacturers to update their labeling with additional warnings, precautions, and other statements about the risk of unintentional injection into blood vessels so that health care providers and patients have a better understanding of the risks.

Source: FDA, May 28, 2015

**Device Recalls**

**Baxter Peripheral Vascular Patches**

Baxter International Inc. recalled nearly 4,000 Vascu-Guard Peripheral Vascular Patches after customers complained of difficulty distinguishing the rough surface from the smooth surface, which was roughened by new packaging. Incorrect orientation of the patch—with the rough side toward the bloodstream—may increase the risk of vessel thrombosis and/or embolism.

Baxter reported 51 complaints and one serious injury. Adverse event reports have included postoperative thrombosis and stroke. “There is an inherent risk of thrombosis associated with vascular procedures in this patient population with underlying vascular diseases,” Baxter notes. “At this point, no causal association has been established.”

The recall affects products 1504026, 1504028, 1504030, and 1504032, distributed from March 16 to May 1, 2015. They are intended for use in peripheral vascular reconstruction, including carotid, renal, iliac, femoral, profunda, and tibial
blood vessels and arteriovenous access revisions. Consumers with questions regarding this class I recall can call Baxter at 1-800-422-9837, Monday through Friday, from 8 a.m. to 5 p.m. Central time.

Sources: Baxter International Inc., June 1, 2015; and FDA, May 29, 2015, and June 5, 2015

**Carefusion Avea Ventilators**

CareFusion is recalling some Avea ventilators because a malfunctioning part may lead over time to development of a “failure mode.” By design, the ventilator activates false Extended High Ppeak or Circuit Occlusion audio and visual alarms, opens the safety valve, and stops working. If this occurs, alternate ventilation support will be needed to reduce the potential of hypoxemia or hypercapnia.

The Avea ventilator is used in health care facilities for continuous breathing support of neonatal through adult patients. The class I recall involves ventilators manufactured, serviced, and distributed from July 1, 2011, to March 15, 2015. A list of affected model and serial numbers is available at the CareFusion website (www.carefusion.com).

CareFusion is contacting customers to initiate on-site corrective action. Customers with questions can call the CareFusion Recall Support Center at 1-888-562-6018 from 6:30 a.m. to 5 p.m. Pacific time.

Source: CareFusion, May 27, 2015

**DEVICE SPOTLIGHT**

**Kunj Gohil, PharmD, RPh**

**Name:** Brio Neurostimulation System  
**Manufacturer:** St. Jude Medical, St. Paul, Minnesota  
**Approval Date:** June 12, 2015  
**Purpose:** This device was developed to help reduce the symptoms of Parkinson’s disease and essential tremor.

**Description:** The Brio Neurostimulation System is an implantable deep-brain stimulation device consisting of a small, battery-powered, rechargeable electrical pulse generator. This system is implanted in the upper chest, beneath the skin, and wire leads connect to electrodes placed within the brain. The generator constantly delivers low-intensity electrical pulses to treat the disease.

**Benefit:** Parkinson’s, which affects approximately one million Americans, occurs when dopamine-producing cells in the brain die or stop making the neurotransmitter. The lack of dopamine impairs a patient’s ability to produce smooth, purposeful movement. This system, the second device approved for Parkinson’s and essential tremor, may give patients an alternative option when medication does not provide adequate symptom relief.

Source: www.fda.gov

**Name:** ENROUTE Transcarotid Stent System  
**Manufacturer:** Silk Road Medical, Inc., Sunnyvale, California  
**Pre-market Approval Date:** May 18, 2015  
**Purpose:** The system is used to reopen narrowed regions of the carotid arteries in the neck, which supply blood to the brain.

**Description:** The device consists of a self-expanding mesh stent made of nitinol tubing and is implanted via a delivery catheter system, the ENROUTE Transcarotid Neuroprotection System (NPS). Together these two devices enable a novel procedure called transcarotid artery revascularization (TCAR).

**Benefit:** TCAR allows for a less-invasive stenting procedure than surgical procedures used for neuroprotection. This first-in-class system allows for direct implantation of a stent into the carotid artery, removing the need to insert the device through the groin. This stent has clinically proven results in more than 10,000 patients across various clinical trials.

Sources: www.fda.gov, www.fierce-medicaldevices.com

**Name:** Ahead 200  
**Manufacturer:**Brainscope, Bethesda, Maryland  
**Approval Date:** May 18, 2015  
**Purpose:** The Ahead 200 is indicated for use as an adjunct to standard clinical practice to aid in the evaluation of patients who are being considered for a computed tomography (CT) scan of the head, but it should not be used as a substitute for a CT scan. It is to be used on patients who sustained a closed head injury within 24 hours, clinically present as having a mild traumatic brain injury (TBI), and are between 18 and 80 years of age.

**Description:** The Ahead 200 is used to record and analyze a patient’s electroencephalograph using a custom sensor attached to a handheld device to provide an interpretation of the structural condition of the patient’s brain after a head injury. This device is used in conjunction with custom smartphone hardware that leverages Google’s Android operating system.

**Benefit:** This device is a smaller, modernized, more rugged version of Brainscope’s previous product, the Ahead 100. The Ahead 200 has the ability to rapidly identify and categorize patients in an urgent-care setting, allowing for improved triage, an increase in lives saved, and a reduction in radiation exposure.

Sources: www.brainscope.com, www.businesswire.com