NEW DRUG APPROVALS
Blincyto for Rare Form of ALL

The FDA has approved blinatumomab (Blincyto, Amgen) to treat patients with Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (B-cell ALL).

Precursor B-cell ALL is a rapidly growing cancer in which the bone marrow makes too many B-cell lymphoblasts. The Philadelphia chromosome is an abnormality that sometimes occurs in the bone marrow cells of leukemia patients.

Blinatumomab is the first FDA-approved drug that engages the body’s T cells to destroy leukemia cells. The drug acts as a connector between the CD19 protein, which is found on the surface of most B-cell lymphoblasts, and CD3, a protein on T-cell lymphocytes. The treatment is meant for patients with relapsed or refractory cancer.

The FDA granted Blincyto breakthrough therapy, priority review, and orphan drug status. Its efficacy and safety were evaluated in a clinical study in which 185 adults with Philadelphia chromosome-negative relapsed or refractory precursor B-cell ALL were treated with blinatumomab for at least four weeks via intravenous infusion. Thirty-two percent of the participants experienced complete remission for approximately 6.7 months.

The product has a boxed warning noting that some clinical trial participants experienced cytokine-release syndrome at the start of the first treatment and brief encephalopathy or other adverse nervous system effects. The most common adverse events with blinatumomab included fever, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, fatigue, constipation, diarrhea, and tremor. The FDA approved Blincyto with a risk evaluation and mitigation strategy.

Source: FDA, December 3, 2014

Lemtrada for Relapsing MS

Alemtuzumab (Lemtrada, Genzyme/Sanoﬁ) has won FDA approval for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety proﬁle, however, it should generally be reserved for patients who have shown an inadequate response to two or more drugs indicated for MS treatment.

The approval was based on two pivotal, randomized, phase 3, open-label, rater-blinded studies that compared alemtuzumab with high-dose subcutaneous interferon (IFN) beta-1a (Rebif, EMD Serono/Pfizer) in patients with relapsing/remitting MS who were either new to treatment (CARE-MS I) or had relapsed on prior therapy (CARE-MS II).

In both trials, alemtuzumab was signiﬁcantly more effective than IFN beta-1a at reducing annualized relapse rates, which were 0.18 versus 0.39, respectively, in CARE-MS I—a 55% relative reduction—and 0.26 versus 0.52 in CARE-MS II—a 49% relative reduction.

Alemtuzumab has a boxed warning for a risk of serious, sometimes fatal autoimmune conditions and a risk of serious and life-threatening infusion reactions. The label also notes that it may cause an increased risk of malignancies. The drug is available only through the Lemtrada Risk Evaluation and Mitigation Strategy.

Lemtrada is administered via intravenous infusion on five consecutive days, with a second course of treatment on three consecutive days 12 months later.

Alemtuzumab is a monoclonal antibody that targets CD52, a protein on T and B cells, which are thought to cause the damaging inflammatory process in MS.

Common adverse effects include rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in an extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. Serious side effects include autoimmune thyroid disease, autoimmune cytophenias, infections, and pneumonitis.

Source: Genzyme Corporation, November 14, 2014

Gardasil 9 to Prevent HPV-Related Cancers

The FDA has approved human papillomavirus 9-valent vaccine, recombinant (Gardasil 9, Merck Sharp & Dohme) to prevent certain cancers caused by human papillomavirus (HPV). The new vaccine covers nine HPV types—five more than the previously approved Gardasil.

The vaccine is approved for use in females ages 9 through 26 years and males ages 9 through 15 years to prevent cervical, vulvar, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58. The vaccine has the potential to prevent approximately 90% of those cancers. Gardasil 9 adds protection against ﬁve HPV types (31, 33, 45, 52, and 58) that cause about 20% of cervical cancers and are not covered by previously approved HPV vaccines. Gardasil 9 is also approved for the prevention of genital warts caused by HPV types 6 or 11.

A randomized, controlled clinical study was conducted in approximately 14,000 females ages 16 through 26 years who tested negative for vaccine HPV types at the start of the study. Participants received either Gardasil or Gardasil 9.

Gardasil 9 was 97% effective in preventing cervical, vulvar, and vaginal cancers caused by HPV types 31, 33, 45, 52, and 58. In addition, Gardasil 9 was as effective as Gardasil in preventing diseases caused by HPV types 6, 11, 16, and 18, based on similar antibody responses. Because of the low incidence of anal cancer caused by the ﬁve additional HPV types, the prevention of anal cancer was based on the demon-
strated 78% effectiveness of Gardasil and on additional antibody data from males and females who received Gardasil 9.

The effectiveness of Gardasil 9 in females and males ages 9 through 14 years was determined in studies that measured antibody responses to the vaccine in approximately 1,200 males and 2,800 females of this age. Their antibody responses were similar to those in females 16 through 26 years of age, so the vaccine is expected to have similar effectiveness in this population.

Gardasil 9 is administered as three injections, with the initial dose followed by shots two and six months later. Its safety was evaluated in approximately 13,000 males and females. The most common adverse reactions were injection-site pain, swelling, redness, and headaches.

Source: FDA, December 10, 2014

**Hysingla ER for Pain**

An abuse-resistant opioid analgesic, extended-release (ER) hydrocodone bitartrate (Hysingla ER, Purdue Pharma), has received FDA approval to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.

Properties of Hysingla ER are expected to reduce but not eliminate abuse when the drug is chewed and then taken orally or crushed and then snorted or injected. The tablet is difficult to crush, break, or dissolve and forms a viscous hydrogel that cannot easily be injected.

Hysingla ER is not approved for as-needed pain relief. Given the risks for abuse, misuse, and addiction, it should be prescribed only to people for whom alternative treatment options are ineffective, are not tolerated, or would be otherwise inadequate to provide sufficient pain management. The available strengths contain 20, 30, 40, 60, 80, 100, and 120 mg of hydrocodone to be taken every 24 hours. Dosages of 80 mg per day and higher should not be prescribed to people who have not previously taken an opioid medication.

The safety and effectiveness of Hysingla ER were evaluated in a clinical study of 905 patients with chronic low back pain. The most common adverse effects were constipation, nausea, fatigue, upper respiratory tract infection, dizziness, headache, and somnolence. Hysingla ER does not raise the serious liver toxicity risks associated with hydrocodone combination products containing acetaminophen; however, taking too much Hysingla ER can cause a potentially fatal overdose.

The FDA is requiring post-marketing studies to assess the effects of Hysingla ER’s abuse-deterrent features on the risks and consequences of abuse.

Source: FDA, November 20, 2014

**Kitabis Pak for Cystic Fibrosis**

The FDA has approved Kitabis Pak (PulmoFlow, Inc.), a copackaging of generic tobramycin inhalation solution with a PARI LC Plus nebulizer for patients with cystic fibrosis (CF).

Kitabis Pak is indicated for the management of CF in adults and pediatric patients 6 years of age and older with *Pseudomonas aeruginosa* infection. The product’s safety and efficacy have not been demonstrated in patients under the age of 6 years, in patients with a forced expiratory volume in one second (FEV1) of less than 25% or greater than 75% predicted, or in patients colonized with *Burkholderia cepacia*.

Tobramycin is an aminoglycoside antibacterial drug produced by *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis, leading to altered cell-membrane permeability, progressive disruption of the cell envelope, and cell death.

In two identically designed, double-blind, randomized, placebo-controlled, parallel-group, 24-week studies, 258 patients ages 6 years and older received tobramycin inhalation solution therapy as outpatients using a PARI LC Plus nebulizer and a DeVilbiss Pulmo-Aide compressor. In both studies, tobramycin inhalation solution led to greater improvement in FEV1 percent predicted relative to baseline compared with placebo—approximately 11% compared with no average change in the first study, and approximately 7% compared with an average decrease of about 1% in the second study.

On average, patients treated with tobramycin inhalation solution compared with placebo were hospitalized less (5.1 days versus 8.1 days) and required less parenteral antipseudomonal antibiotic treatment (9.6 days versus 14.1 days).

Sources: Pipeline Review, December 3, 2014, and Kitabis Pak prescribing information

**Onexton Gel for Acne Vulgaris**

A combination of 1.2% clindamycin and 3.75% benzoyl peroxide (Onexton Gel, Valeant Pharmaceuticals International, Inc.) has received FDA approval for once-daily treatment of noninflammatory and inflammatory acne vulgaris in patients 12 years of age and older.

Onexton Gel’s efficacy was studied in a pivotal trial involving 498 patients with moderate-to-severe acne. At week 12, Onexton Gel reduced noninflammatory lesions by a mean of 52% and inflammatory lesions by a mean of 60% compared with reductions of 28% and 31%, respectively, in subjects given vehicle. The proportion of patients experiencing treatment success (defined as at least a two-grade improvement in the Evaluator Global Severity score from baseline) was 35% in the Onexton group compared with 17% in the vehicle group.

The most common treatment-emergent and treatment-related adverse events (AEs) included a burning sensation, contact dermatitis, pruritus, and rash (each 0.4%). Serious AEs, including colitis and allergic reactions, have been reported.
with the use of combination clindamycin/benzoyl peroxide products.

Source: Valeant Pharmaceuticals, November 25, 2014

**Generic Approvals**

**Three Firms Offer Celecoxib**

Three companies now offer generic celecoxib. Mylan Inc., Actavis PLC, and Lupin Pharmaceuticals Inc. (which makes an authorized generic) are selling 50-mg, 100-mg, 200-mg, and 400-mg capsules, which according to IMS Health have U.S. sales of about $2.5 billion a year as Pfizer’s Celebrex. A federal appeals court ruling issued December 16 prevents Teva Pharmaceutical Industries Ltd. from bringing its generic celecoxib to market until June.

Celecoxib is indicated for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, and for the management of acute pain in adults.

Sources: Actavis PLC and Mylan Inc., December 10, 2014; Pharma Major Lupin Ltd., December 11, 2014; and Fierce-Pharma, December 17, 2014

**Prednisolone Sodium Phosphate Orally Disintegrating Tablets**

The first generic version of Shionogi’s Orapred ODT has been launched by Mylan Inc. Prednisolone sodium phosphate orally disintegrating tablets, available in 10 mg, 15 mg, and 30 mg, are indicated as an anti-inflammatory or immunosuppressive agent for certain conditions; for the treatment of certain endocrine conditions; and for palliation of certain neoplastic conditions.

Source: Mylan Inc., December 11, 2014

**Allegra Generics**

The FDA says it has approved the first generics of two formulations of Allegra.

Actavis Mid Atlantic, LLC, won approval to market children’s fexofenadine hydrochloride oral suspension for allergy and for hives, 30 mg/5 mL, the generic version of Children’s Allegra Allergy and Children’s Allegra Hives.

Dr. Reddy’s Laboratories, Ltd., can now market fexofenadine hydrochloride and pseudoephedrine hydrochloride extended-release tablets USP 60 mg/120 mg (allergy and congestion, 12-hour formulation), an over-the-counter version of Allegra-D extended-release tablets.

Source: FDA, November 18, 2014

**Bimatoprost 0.03%**

Apotex Inc. has received FDA approval for the first generic version of bimatoprost 0.03% ophthalmic solution (Latisse, Allergan). Latisse is a prostaglandin analog indicated to treat hypotrichosis of the eyelashes by increasing their growth, including length, thickness, and darkness.

Sources: FDA, December 1, 2014, and Latisse prescribing information

**NEW INDICATIONS**

**Avastin Plus Chemotherapy In Some Ovarian Cancer Cases**

Bevacizumab (Avastin, Roche) is now FDA-approved in combination with chemotherapy for the treatment of some ovarian cancer cases.

The approval was based on the phase 3, open-label AURELIA study in 361 women who were randomly assigned to one of six treatment arms (paclitaxel, topotecan, or liposomal doxorubicin with or without bevacizumab). Bevacizumab plus chemotherapy improved median progression-free survival (PFS) by 62% compared with chemotherapy alone (6.8 months versus 3.4 months). Study participants had platinum-resistant, recurrent, epithelial ovarian, fallopian tube, or primary peritoneal cancer and had received no more than two prior chemotherapy regimens; the new indication applies to this population and calls for the use of bevacizumab with paclitaxel, pegylated liposomal doxorubicin, or topotecan chemotherapy.

In the study, grade 3 or 4 adverse events occurring at a higher incidence with bevacizumab plus chemotherapy compared with chemotherapy alone included hypertension (6.7% versus 1.1%) and hand-and-foot syndrome (4.5% versus 1.7%).

Bevacizumab is an antibody that targets and inhibits vascular endothelial growth factor (VEGF), a key driver of tumor growth. This allows bevacizumab to be combined with a broad range of chemotherapies and other anticancer treatments.

Source: Roche, November 17, 2014

**Cyramza for NSCLC**

Ramucirumab (Cyramza injection, Eli Lilly) has won FDA approval for use in combination with docetaxel for the treatment of patients with metastatic non–small-cell lung cancer (NSCLC) that has progressed on or after platinum-based chemotherapy. In patients with EGFR or ALK genomic tumor aberrations, the use of ramucirumab should occur after disease progression on FDA-approved therapy that addresses those aberrations.

Ramucirumab was previously approved as monotherapy and in combination with paclitaxel for the treatment of patients with advanced gastric or gastroesophageal junction adenocarcinoma after disease progression on first-line therapy.

The latest approval was based on the demonstration of improved overall survival (OS) in a multicenter, double-blind, placebo-controlled study that enrolled 1,253 patients with previously treated metastatic NSCLC. Patients were randomized to receive either ramucirumab (10 mg/kg every three weeks) in combination with docetaxel (75 mg/m² every three weeks) on day 1 of a 21-day cycle or matching placebo plus docetaxel.

Median OS was significantly longer in the ramucirumab plus docetaxel arm than in the placebo plus docetaxel arm (10.5 months versus 9.1 months). Progres-
sion-free survival was also significantly longer for patients receiving ramucirumab plus docetaxel (hazard ratio, 0.76).

The most frequently reported adverse reactions with ramucirumab plus docetaxel were neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation. The most common serious adverse reactions with ramucirumab plus docetaxel were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%).

Source: FDA, December 12, 2014

**Invega Sustenna for Schizoaffective Disorder**

The once-monthly atypical long-acting antipsychotic paliperidone palmitate (Invega Sustenna, Janssen Pharmaceuticals) has received FDA approval for the treatment of schizoaffective disorder (SD) as monotherapy or adjunctive therapy.

The FDA's approval (which followed a priority review) was based on data from a 15-month period in a long-term maintenance study that measured the ability of Invega Sustenna to delay relapse in SD patients. Treatment with Invega Sustenna resulted in a statistically significant delay in relapse due to mood (depression and mania) and psychotic symptoms of SD compared with placebo. The trial, which included a six-month open-label treatment period and a 15-month double-blind period, was the first registration study to investigate maintenance treatment with a long-acting injectable in SD patients.

Invega Sustenna, the only once-monthly medication indicated to treat SD as monotherapy, is also indicated for SD as adjunctive therapy to mood stabilizers or antidepressants. SD is generally treated with a combination of medications.

The most common adverse events observed with Invega Sustenna included injection-site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder.

Source: Janssen, November 13, 2014

**Jakafi for Polycythemia Vera**

Ruxolitinib (Jakafi, Incyte Corporation) has become the first drug approved by the FDA to treat patients with polycythemia vera (PV). Ruxolitinib, indicated for PV patients who have had an inadequate response to or are intolerant of hydroxyurea, is also FDA-approved for the treatment of intermediate- or high-risk myelofibrosis, a closely related blood cancer.

PV is a myeloproliferative neoplasm typically characterized by elevated hematocrit, which can lead to an increased risk of blood clots, as well as elevated white blood cell and platelet counts. Current standard treatment is phlebotomy plus aspirin. When phlebotomy can no longer control PV, chemotherapy is used. Approximately 25% of patients with PV are considered uncontrolled because they have shown an inadequate response to or are intolerant of hydroxyurea, the most commonly used chemotherapeutic agent for the disorder.

Ruxolitinib is a Janus kinase 1 (JAK1) and JAK2 inhibitor that targets overactive JAK pathway signalling, which plays a critical role in the development of both PV and myelofibrosis.

The new approval was based on the pivotal phase 3 RESPONSE trial. Patients treated with ruxolitinib demonstrated superior hematocrit control and reductions in spleen volume compared with best available therapy. In addition, a greater proportion of patients in the ruxolitinib arm achieved complete hematological remission (defined as achieving hematocrit control and lowering platelet and white blood cell counts). The most common hematological adverse events (AEs) were thrombocytopenia and anemia. The most common nonhematological AEs included headache, abdominal pain, diarrhea, dizziness, fatigue, pruritus, dyspnea, and muscle spasms.

Source: Incyte Corporation, December 4, 2014

**Xgeva for Hypercalcemia Of Malignancy**

The FDA has approved denosumab (Xgeva, Amgen) for the treatment of hypercalcemia of malignancy (HCM) refractory to bisphosphonate therapy.

The decision was based on an open-label, single-arm study that enrolled patients with advanced cancer and persistent hypercalcemia after recent bisphosphonate treatment. At day 10 after the first dose of denosumab, 63.6% of the 33 patients evaluated showed a clinical response (albumin-corrected serum calcium [CSC] levels of 11.5 mg/dL [2.9 mmol/L] or less). The complete response (a CSC of 10.8 mg/dL [2.7 mmol/L] or less) by day 10 was also 63.6%.

The estimated median time to response (CSC of 11.5 mg/dL or less) was nine days, and the median duration of response (the number of days from the first occurrence of CSC of 11.5 mg/dL or less) was 104 days. The most common adverse reactions included nausea, dyspnea, decreased appetite, headache, peripheral edema, vomiting, anemia, constipation, and diarrhea.

In HCM patients, denosumab is administered as a subcutaneous injection (120 mg) every four weeks, with additional 120-mg doses on days 8 and 15 of the first month of therapy.

By binding to RANK ligand (RANKL), a protein essential for the formation, function, and survival of osteoclasts, denosumab modulates the release of calcium from bone. The drug prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, resulting in decreased bone destruction and calcium release.

Source: Amgen, December 8, 2014

**Priftin for Latent TB**

The FDA has approved rifapentine (Priftin, Sanofi) in combination with isoniazid for the treatment of latent tuberculosis infection (LTBI) in patients
2 years of age and older at high risk of progression to TB disease. Rifapentine is an antimycobacterial agent that has been approved since 1998 for use in combination with one or more anti-TB drugs for the treatment of active pulmonary TB caused by *Mycobacterium tuberculosis*.

A person with LTBI is infected with the bacteria that cause TB but does not feel sick, have symptoms, or risk spreading the bacteria to others. Approximately 5% to 10% of U.S. individuals with LTBI will develop TB if not treated.

The new approval was based partly on the PREVENT TB study, which compared a 12-week, once-weekly regimen of rifapentine plus isoniazid with nine months of self-administered daily isoniazid alone. TB developed in five of 3,074 patients randomly assigned to the rifapentine/isoniazid group (cumulative rate, 0.16%) compared with 10 of 3,074 patients in the isoniazid group (cumulative rate, 0.32%).

The new indication applies to LTBI caused by *M. tuberculosis* in patients at high risk of progression to TB disease (including those in close contact with active TB patients; persons with a recent conversion to a positive tuberculin skin test; human immunodeficiency virus–infected patients; or patients with pulmonary fibrosis on radiographs). Rifapentine must always be used with isoniazid as a 12-week, once-weekly regimen for the treatment of LTBI.

Source: Sanofi, December 2, 2014

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**Ixazomib for Amyloidosis**

Ixazomib (MLN9708, Takeda Pharmaceutical Company Ltd.) has received FDA breakthrough therapy status for the treatment of relapsed or refractory systemic light-chain (AL) amyloidosis. The development program for the investigational, oral proteasome inhibitor in this indication progressed directly from a phase 1 to a phase 3 clinical trial, TOURMALINE-AL, which is evaluating ixazomib plus dexamethasone in patients with relapsed or refractory AL amyloidosis.

AL amyloidosis is a rare and aggressive protein-misfolding disorder characterized by the deposition of amyloid in bodily organs and tissues. There are no approved treatments, and ixazomib has also received orphan drug designation for AL amyloidosis.

Source: Takeda Pharmaceutical Company Ltd., December 1, 2014

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**Dupilumab for Atopic Dermatitis**

The FDA has granted a breakthrough therapy designation to dupilumab (Regeneron Pharmaceuticals/Sanofi) for the treatment of adults with moderate-to-severe atopic dermatitis (AD) who are not adequately controlled with topical prescription therapy or for whom those treatments are not appropriate.

The designation is based on positive results from phase 1 and 2 clinical trials. A phase 3 clinical program is under way. Dupilumab, an investigational fully human monoclonal antibody, is directed against the shared interleukin (IL)-4 receptor alpha subunit, which blocks signaling from both IL-4 and IL-13. IL-4 and IL-13 are key cytokines that are required for the initiation and maintenance of the type 2 helper T-cell immune response, which is believed to be a critical pathway in allergic inflammation.

Source: Regeneron Corporation, November 20, 2014

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**Fast-Track Designations**

**RSV Vaccine Candidate**

The FDA has given fast-track status to a respiratory syncytial virus (RSV) F-protein nanoparticle vaccine candidate for the protection of infants via maternal immunization. The vaccine, being developed by Novavax, Inc., would be given to pregnant women, who would transfer antibodies to the unborn child via the placenta.

Novavax has completed two clinical studies of its RSV F vaccine in women of childbearing age. In September 2014, Novavax initiated another study to evaluate the safety and immunogenicity of the vaccine in pregnant women; quantify the transfer of vaccine-induced RSV antibodies to infants; and assess the safety and RSV-specific antibody levels in infants through 1 year and 6 months of life, respectively.

Source: Novavax, Inc., November 20, 2014

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**GC021109 for Alzheimer’s Disease**

GliaCure’s candidate for Alzheimer’s disease treatment, GC021109, has received FDA fast-track status. GC021109 is a small molecule that in preclinical studies has demonstrated two primary actions downstream of target engagement: the stimulation of phagocytosis and anti-inflammatory actions in which levels of pro-inflammatory cytokines are reduced.

A first-in-human phase 1a study of GC021109 began in September 2014. GliaCure is planning a phase 1b trial, a multiple ascending dose study in **continued on page 22**
The FDA has approved new labeling standards for information about using prescription drugs and biological products during pregnancy and breastfeeding. The letter categories A, B, C, D, and X are used to classify the risks of prescription use during pregnancy will be replaced with three detailed subsections that describe risks in the real-world context of caring for pregnant women who may need medications.

“Prescribing decisions during pregnancy and lactation are individualized and involve complex maternal, fetal, and infant risk–benefit considerations. The letter category system was overly simplistic and was misinterpreted as a grading system, which gave an oversimplified view of the product risk,” said Sandra Kweder, MD, Deputy Director of the Office of New Drugs in the FDA’s Center for Drug Evaluation and Research. “The new labeling rule provides explanations, based on available information, about the potential benefits and risks for the mother, the fetus, and the breastfeeding child.”

The rule requires the use of three subsections in the labeling titled “Pregnancy,” “Lactation,” and “Females and Males of Reproductive Potential.” These subsections must include a summary of the risks of using a drug during pregnancy and breastfeeding, a discussion of the data supporting the summary, and relevant information to help health care providers make prescribing and counseling decisions.

The rule finalizes many provisions of an FDA proposal issued in May 2008 and will take effect on June 30, 2015. After that, new drugs and biological products must use the new format immediately, while the requirements will be phased in gradually for previously approved products. Source: FDA, December 2, 2014

**Actimab-A for AML in Elderly Named an Orphan Drug**

Actimab-A (Actinium Pharmaceuticals, Inc.) has received an FDA orphan-drug designation for the treatment of newly diagnosed acute myeloid leukemia (AML) in patients more than 60 years of age. Actimab-A, an alpha radiolabeled antibody, is the subject of a multicenter phase 1/2 clinical trial. Interim data show that median overall survival of the seven secondary AML patients (with prior myelodysplastic syndrome) in the study was 9.1 months, which compares favorably to historical norms of two to five months depending on the treatment modality. Source: Actinium Pharmaceuticals, Inc., December 1, 2014

**Priority Review for Eylea for Diabetic Retinopathy in DME**

The FDA has granted priority review to an application to approve aflibercept injection (Eylea, Regeneron Pharmaceuticals, Inc.) for the treatment of diabetic retinopathy in patients with diabetic macular edema (DME). The Prescription Drug User Fee Act goal date is March 30, 2015. The drug was previously designated a breakthrough therapy for this indication. The application is supported by data from the phase 3 VIVID-DME and VISTA-DME trials, which included a prespecified secondary endpoint evaluating diabetic retinopathy based on an established grading scale in patients with DME. Source: Regeneron Pharmaceuticals, Inc., December 1, 2014

**FDA Alters Pregnancy Labels**

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**Tecfidera Warning**

The label for the multiple sclerosis drug dimethyl fumarate (Tecfidera, Biogen Idec) is being updated to describe a single fatal case of the rare and serious brain infection progressive multifocal leukoencephalopathy (PML).

The FDA says patients taking dimethyl fumarate should contact their health care professionals right away if they experience symptoms that concern them, such as new or worsening weakness; trouble using their arms or legs; or changes to thinking, eyesight, strength or balance. Health care professionals should stop dimethyl fumarate if PML is suspected.

Dimethyl fumarate can benefit patients with relapsing forms of multiple sclerosis (MS). The patient who died had taken dimethyl fumarate for more than four years and was not taking any other drugs that affect the immune system or drugs that are thought to be associated with PML. This is the only confirmed case of PML reported in patients taking dimethyl fumarate.

PML is caused by the John Cunningham ham virus, which is common and harmless in most people but can cause PML in some patients with weakened immune systems. It can lead to severe disability or death.

Prior to developing PML, the patient had a very low lymphocyte count. It is unknown whether this contributed to the development of PML in this patient, or if low lymphocyte counts are a risk factor for PML in dimethyl fumarate patients. Source: FDA, November 25, 2014

**Ziprasidone Is Associated With Potentially Fatal Skin Reaction**

The antipsychotic ziprasidone (Geodon, Pfizer, and generics) is associated with a rare but serious skin reaction that can spread to other parts of the body, the FDA says. A new warning has been added to ziprasidone’s labeling about the condition, called “drug reaction with eosinophilia and systemic symptoms” (DRESS).

Ziprasidone is used to treat schizophrenia and bipolar I disorder. In 2013, approximately 2.5 million prescriptions for oral ziprasidone were dispensed. DRESS may start as a rash that can spread to all parts of the body. It can
include fever, swollen lymph nodes, and inflammation of organs, such as the liver, kidney, lungs, heart, or pancreas. DRESS also causes a higher-than-normal number of eosinophils in the blood. Health care professionals should stop ziprasidone treatment immediately if DRESS is suspected.

The FDA reviewed six worldwide cases of DRESS that were associated with ziprasidone use; times to the onset of symptoms ranged from 11 days to one month after ziprasidone initiation. In three cases, symptoms recurred after the discontinuation and re-initiation of ziprasidone, with a faster onset following re-initiation. Three of the cases included concomitant use of drugs associated with DRESS. The cases reported serious outcomes, including hospitalization. Although the reported cases included no fatalities, DRESS has a mortality rate of up to 10%.

The pathogenesis of DRESS is unclear; however, it is thought to result from a combination of genetic and immunological factors, such as detoxification defects in the drug-metabolism pathway, resulting in toxic metabolite formation and an immune response. Reactivation of herpes virus or Epstein-Barr virus infections may also play a role by inducing or amplifying the immune reaction.

DRESS has no specific treatment. The keys to managing it are early recognition, discontinuation of the offending agent as soon as possible, and supportive care. Treatment with systemic corticosteroids should be considered in cases with extensive organ involvement.

Source: FDA, December 11, 2014

**Medication Recalls**

**Northstar 300-mg Gabapentin**

Aurobindo Pharma USA, Inc., recalled lot GESB14011-A of Northstar gabapentin capsules USP, 300 mg, after receiving four complaints about empty capsules. The lot, which expires in December 2015, is packaged in bottles of 100. Those with questions can contact the company’s Pharmacovigilance group at 732-839-9400, option 2, Monday through Friday, 8:30 a.m. to 5 p.m. Eastern time.

Source: Aurobindo Pharma USA, November 23, 2014

**Baxter Potassium Chloride Injection**

Baxter International Inc. recalled lot P319160 of highly concentrated potassium chloride injection, 10 mEq per 100 mL, because some containers were mislabeled on the overpouch as highly concentrated potassium chloride injection, 20 mEq per 100 mL.

The inability to detect this mislabeling at the point of care may result in administration of a dose lower than intended, which may have serious consequences in patients prone to severe electrolyte imbalance. The product, distributed in the U.S. from June 23, 2014, to October 2, 2014, expires June 30, 2015. To return it, contact Baxter Healthcare Center for Service at 1-888-229-0001, Monday through Friday, 7 a.m. to 6 p.m. Central time.

Source: FDA, November 21, 2014

**RESEARCH BRIEFS**

**U.S. Health Spending Growth In 2013 Is Lowest Since 1960**

National health spending grew 3.6% in 2013, the lowest annual increase since the Centers for Medicare and Medicaid Services (CMS) began tracking the statistic in 1960, officials reported in *Health Affairs*. Spending slowed for private health insurance, Medicare, hospitals, physicians, clinical services, and out-of-pocket spending by consumers but accelerated for Medicaid and prescription drugs.

Health care spending has grown at historically low rates for the past five years, consistent with declines generally seen during economic downturns. Looking ahead, “the key question is whether health spending growth will accelerate once economic conditions improve significantly; historical evidence suggests that it will,” the authors noted.

They pointed out, however, that in the near term the health sector will “undergo major changes that will have a substantial impact” on consumers, providers, insurers, and sponsors of health care. These result from the creation of online marketplaces by the Patient Protection and Affordable Care Act, its expansion of Medicaid, and restraints the act placed on Medicare, the analysts found.

The study found that health care spending rose to $2.9 trillion, or $9,255 per person, in 2013. As a share of gross domestic product, health care remained at 17.4%, unchanged since 2009. Spending increases in 2013 included: Medicare, 3.4%; Medicaid, 6.1%; private health insurance premiums, 2.8%; consumer out-of-pocket spending, 3.2%; physician and clinical services, 3.8%; hospital care, 4.3%; and retail prescription drugs, 2.5%.

Source: Kaiser Health News, December 3, 2014

**Drug Costs Up 12% in 2014**

U.S. spending on medications increased by an estimated 11.7% in 2014—pushing the nation’s drug bill above $375 billion, according to a report by the IMS Institute for Healthcare Informatics.

Several factors drove the spending spike, including the introduction of costly new hepatitis C virus (HCV) treatments and a dip in drug-patent expirations that typically lead to savings as cheaper generics replace brand-name drugs. During the previous five years, annual drug spending increased an average of 3.6%.

The report anticipates that spending increases will slow to 7% to 9% in 2015 and 3% to 5% in 2016 as the impact of new HCV drugs declines, as less expensive biosimilar products become available, and as several brand-name drugs lose patent protection.
A New Drug Costs $2.6 Billion

Developing a new prescription medicine that gains marketing approval—a process often lasting more than a decade—costs an estimated $2.558 billion, according to the Tufts Center for the Study of Drug Development. The price tag includes an average out-of-pocket cost of $1.395 billion and time costs (expected returns that investors forego while a drug is in development) of $1.163 billion.

An estimated average $312 million in post-approval research and development (R&D)—studies to test new indications, new formulations, and new dosage strengths and regimens, and to monitor safety and long-term side effects in patients as a condition of FDA approval—boosts the full product lifecycle cost per approved drug to $2.870 billion in 2013 dollars.

In a study published in 2003, Tufts estimated the cost per approved new drug at $802 million (in 2000 dollars) for drugs first tested in humans from 1983 to 1994. That cost equals $1.044 billion in 2013 dollars, indicating that the cost to develop and win marketing approval for a new drug rose by 145% between the two study periods.

Rising development costs have been driven mainly by increases in out-of-pocket costs for individual drugs and higher failure rates for drugs tested in humans. Factors that likely have boosted out-of-pocket costs include larger, more complex clinical trials; higher costs of input from the medical sector used for development; greater focus on chronic and degenerative diseases; changes in protocol designs aimed at gathering health technology assessment information; and testing to accommodate payer demands for comparative effectiveness data.

Antibiotic Failure Rates Rise

The failure rate of initial antibiotic monotherapies prescribed by primary care physicians in the United Kingdom rose from 13.9% in 1991 to 15.4% in 2012, according to researchers from Cardiff University and the University of Oxford.

Using data on 58 million antibiotic prescriptions from the Clinical Practice Research Datalink (a database derived from nearly 700 primary care practices), the researchers analyzed nearly 11 million monotherapy episodes for four indications: upper respiratory tract infections, lower respiratory tract infections, skin and soft tissue infections, and acute otitis media. Of all antibiotic prescriptions, 98% were monotherapy.

Over time, the proportion of infections treated with antibiotics changed. The greatest increase was in acute otitis media; antibiotic treatment rose from 63% in 1991 to 83% in 2012. The proportion of upper respiratory tract infections treated with antibiotics fell from 59% in 1991 to 55% in 2012. The most commonly prescribed antibiotics were amoxicillin, penicillin-V, and floxacillin.

Trimethoprim’s failure rate increased from 24.7% in 1991 to 55.9% in 2012 when used to treat upper respiratory tract infections. Failure rates for cephalosporins increased “markedly.” Failure rates for macrolides remained largely stable. In 2012, the antibiotics with the lowest failure rates were penicillin-V for upper respiratory tract infections and lymecycline and oxytetracycline for skin and soft tissue infections.

The rise in antibiotic failures was less prominent with the most frequently prescribed antibiotics and those recommended as first-line treatments for infections, such as amoxicillin, clarithromycin, and erythromycin. The more striking increases seen in antibiotics not usually recommended as first-line treatments for the infection classes in the study, such as cephalosporins.

Source: BMJ, September 2014

Candida-Related Septic Shock

The microbial cause of infection is often unknown when antibiotics are prescribed for patients in Candida-related septic shock, but delaying therapy has been associated with a mortality rate of more than 90%. Researchers from Barnes-Jewish Hospital conducted a pilot study that found empiric antifungal treatment could shorten the time to administration of appropriate therapy.

In the Barnes-Jewish Intensive Care Unit (ICU), Candida causes 10% of septic shock cases. The rate of resistance to fluconazole in all species of Candida combined is about 15%.

In this before-and-after study, 15 patients who presented before 2013 made up the standard-care group. They received antibiotics, including antifungal continued on page 28
drugs, at the discretion of the treating physician. Thirteen patients treated after January 1, 2013, received empiric therapy with micafungin 100 mg daily or fluconazole 800 mg intravenously (IV) on day 1, followed by 400 mg IV daily. The choice of antifungal agent was left to the ICU team and clinical pharmacist but was partly based on whether the patient had any prior exposure to fluconazole, in which case micafungin was prescribed.

Sixteen patients received appropriate antifungal therapy. The other 12 received delayed antifungal therapy (one received no antifungal therapy before death).

In the empiric therapy group compared with the standard care group, the mean time from onset of shock to appropriate therapy (10.6 hours versus 40.5 hours) and the mean time from culture collection to appropriate therapy (13.7 hours versus 43.3 hours) were shorter. Patients who received appropriate therapy within 24 hours of onset of hypotension had greater hospital survival rates: 68.8% versus 41.7%.

Source: *Clinical Therapeutics*, September 2014

**Oxaliplatin and Lhermitte’s Sign**

Lhermitte’s sign, a neuropathic symptom commonly associated with multiple sclerosis, may also be a side effect of oxaliplatin therapy, according to a case report by clinicians from Western Michigan University and Bronson Methodist Hospital.

Their patient, a 50-year-old man with stage III colorectal cancer, underwent a laparoscopic low anterior resection. Because of his busy work schedule, his physicians treated him with capecitabine and oxaliplatin (CAPEOX) rather than the treatment recommended by the National Comprehensive Cancer Network guidelines: six months of adjuvant chemotherapy with 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX). FOLFOX uses 85 mg/m² of oxaliplatin every two weeks, while CAPEOX uses 130 mg/m² of oxaliplatin every three weeks.

After seven cycles of chemotherapy, the patient developed severe electric-shock–like pain that shot down his back and extremities when he bent his neck. He also had a slight tingling and numbness in his upper arms and fingertips. A thorough history and examination revealed a classic Lhermitte’s sign on neck flexion. Oxaliplatin was discontinued and he was switched to capecitabine to complete six months of adjuvant chemotherapy. Six months after the oxaliplatin was stopped, his symptoms resolved.

Lhermitte’s phenomenon due to chemotherapy is rare, the authors say, but polyneuropathy is a common side effect of high-dose oxaliplatin. The onset of Lhermitte’s sign can be delayed by weeks to months. The usual cause is cisplatin or oxaliplatin, but it has also been seen in regimens that include docetaxel, cyclophosphamide, and fludarabine.

The researchers say it isn’t clear whether capecitabine could have a role in causing or potentiating Lhermitte’s sign. But because capecitabine is being used more often instead of 5-fluorouracil with oxaliplatin in colorectal cancer, they caution, neurological side effects could happen more frequently.

Source: *Clinical Colorectal Cancer*, September 2014

**Venous Thromboembolism Is Up**

Methods of identifying and treating venous thromboembolism (VTE) have improved in the last two decades—and yet the annual event rate of VTE is rising, say researchers from the University of Massachusetts and McMaster University. Is this because diagnostic methods have improved, or prevention and treatment strategies are falling short?

Maybe both, the researchers conclude. Clinicians are “clearly detecting more cases” than they were before the introduction of computed tomography pulmonary angiography. And between 1985 and 2009, the use of noninvasive diagnostic methods for detecting VTE increased from about two-thirds of patients to nearly all patients. But the researchers question how much of the increase in cases reflects small, clinically insignificant pulmonary embolisms.

This population-based surveillance study of VTE is based on data from 5,487 residents of Worcester, Massachusetts, who participated in the long-running Worcester VTE study.

Between 1985 and 2009, 5,025 patients were diagnosed with acute pulmonary embolism or lower-extremity deep vein thrombosis. Of those, 3,887 had VTE for the first time and 1,138 had recurrent VTE. The proportion of first-time VTE increased from about two-thirds in the initial cohort to approximately 80% in the 2009 cohort. The rate of recurrent VTE dropped from 39 per 100,000 in 1985–1986 to 19 in 2003, then rebounded to 35 in 2009.

After adjustment for sex and age, the annual VTE event rate rose from 112 per 100,000 in 1985–1986 to 168 in 2009. That makes VTE a “major national health problem with a substantial disease burden,” the study concluded—and given the aging U.S. population, that burden is expected to more than double by 2050.

Source: *American Journal of Medicine*, September 2014

**Age, Gender in Colorectal Cancer**

The incidence of colorectal cancer (CRC) increases with age, and gender also plays a part—yet age- and gender-related factors have not been fully investigated, University of Tokyo researchers say. To clarify these clinical and pathological features, the researchers evaluated data on 632 men and 427 women with CRC admitted to the University of Tokyo Hospital over seven years.

Of the 1,059 patients, 1,036 underwent
suggest the importance in colorectal carcinoma. The results of their study instability (MSI) with the serrated neoplasms, and microsatellite dominantly associated with the adenoma-chromosomal instability (CIN) is pre-

ing and with more concomitant adenomas tended to be older. In women, the histological type was the only variable associated with age.

In the univariate analysis, tumor location was associated with age in both sexes. The shift of tumor location to the proximal colon with increasing age was more prominent in women: Only 11% of women younger than 50 years of age had right-sided CRC, compared with nearly half of those older than 80 years. In multivariate analysis, right-sided CRC was the only independent variable that correlated with an age greater than 70 years among women.

The correlation between number of concomitant adenomas and age was stronger in men, whose number of concomitant adenomas gradually increased with age. Among patients older than 70 years, 43% of men had one or more concomitant adenomas, compared with 31% of women. With increasing age, the proportion of proximal CRC gradually increased in women, while that of rectal cancer gradually decreased.

The higher incidence of concomitant adenomas and the shift for proximal predominance are the age-related characteristics of CRC in elderly patients, the researchers conclude. They note that chromosomal instability (CIN) is predominantly associated with the adenoma-carcino sequence, and microsatellite instability (MSI) with the serrated neoplastic pathway. The results of their study suggest the importance in colorectal car-

cinogenesis of CIN in elderly men and MSI in elderly women, the researchers say. Source: Clinical Colorectal Cancer, December 2014

USPSTF Doesn’t Recommend Vitamin D Screening

There isn’t enough evidence to determine whether the benefits of screening adults for vitamin D deficiency outweigh the potential harm, the U.S. Preventive Services Task Force (USPSTF) says. The USPSTF’s decision applies to generally healthy adults who do not have signs or symptoms of vitamin D deficiency. It does not apply to people who have conditions that require extra vitamin D, pregnant women, or people who live in nursing homes.

The task force identified areas where additional research is needed to make a future recommendation for or against vitamin D deficiency screening. For example, more research is needed to create a clearer understanding of how to define vitamin D deficiency, and to determine the accuracy of screening tests.

Sources: USPSTF, November 25, 2014

Narcotic Painkiller Deaths Triple

Fatal overdoses involving prescription painkillers such as oxycodone (OxyContin, Purdue Pharma) and hydrocodone bitartrate/acetaminophen (Vicodin, AbbVie) tripled between 1999 and 2012, according to a report from the Centers for Disease Control and Prevention (CDC).

However, in the last year of the study (2011–2012), the CDC noted a 5% drop in deaths. Other CDC data show that while the rate of fatal overdoses is still increasing, it is not increasing as fast as it did between 2000 and 2006.

In the new report, researchers using the CDC’s National Vital Statistics System found that, after adjusting for age, fatal overdoses involving prescription narcotic painkillers increased from 1.4 cases per 100,000 people in 1999 to 5.1 cases per 100,000 people in 2012. Kentucky, Nevada, New Mexico, Utah, and West Virginia were hit hardest.

Health officials have moved to curb the spread of narcotic-painkiller abuse. Certain forms of these drugs, such as hydrocodone, have become harder to get because of changes by the FDA, which has also approved abuse-deterrent forms that are difficult to crush or dissolve to inhibit snorting or injecting them.

The CDC report also noted that the rate of drug-poisoning deaths involving heroin nearly tripled, from 0.7 deaths per 100,000 in 1999 to 1.9 in 2012. The upsurge in heroin-related deaths shows no signs of slowing.

Sources: Medical Xpress, December 2, 2014, and CDC, December 2014

DEVICE NEWS
SAVI Scout Surgical Guidance System Approved for Marketing

The FDA has approved marketing of the SAVI Scout surgical guidance system (Cianna Medical Inc.), which uses real-time audible and visual indicators to give surgeons a precise way to target tissue during lumpectomy and excisional biopsy procedures.

The system uses nonradioactive electromagnetic wave technology to detect a reflector that can be placed in the target tissue up to seven days prior to surgery. During the procedure, the surgeon then uses the SAVI Scout handpiece, which emits infrared light and electromagnetic waves, to locate the reflector and plan the incision. The surgeon then removes the reflector and the target tissue.

A pilot study of 24 patients evaluated placement, localization, and retrieval of the SAVI Scout and reported 100% surgical success. In all cases, the target tissue and reflector were successfully removed; there were no incidents of reflector migration or adverse events.
Pathology reports showed clear margins in numbers comparable to radioactive seed location.

The standard preoperative technique for localizing nonpalpable breast lesions is wire localization. With this procedure, a wire is inserted into the breast by a radiologist to guide the surgeon to the target tissue. The time between wire placement and surgery can be several hours and, in addition to being potentially unpleasant for women, the process presents scheduling challenges for surgeons, radiologists, and hospital staff. With SAVI Scout, the reflector can be placed comfortably several days prior to surgery, on the day of surgery by a radiologist, or in the operating room by a surgeon.

Source: Cianna Medical Inc., December 10, 2014

Noninvasive Test for Coronary Artery Disease

HeartFlow Inc. has received de novo clearance from the FDA for FFR_CTi, its noninvasive imaging technology for coronary artery disease that offers insight into the extent of the blockage and whether it is impacting blood flow.

The platform marries noninvasive imaging with computational fluid dynamics technology to produce detailed models of a patient’s cardiovascular anatomy. The technology is cleared for the evaluation of patients showing signs and symptoms of coronary artery disease in conjunction with other clinical patient data.

Noninvasive tests are widely used as a first-line method to diagnose coronary artery disease, but studies have shown a need to improve their accuracy. A study by Duke University investigators found that fewer than 38% of patients who underwent elective invasive cardiac catheterization and angiography were found to have obstructive coronary artery lesions, even though noninvasive testing had been performed on 84% of those patients.

HeartFlow’s FFR_CTi technology solves millions of complex equations simulating blood flow in the coronary arteries to provide mathematically computed fractional flow reserve values from images derived using noninvasive computed tomography angiography. Fractional flow reserve values demonstrate blood pressure differences around a lesion to determine whether it is likely to reduce blood flow to the heart.

Clinical data from the HeartFlow NXT study demonstrated superior discriminatory ability to identify lesions that have the potential to impede blood flow when compared to coronary CT angiography alone. In the study, published in the Journal of the American College of Cardiology earlier this year, FFRCT had higher diagnostic accuracy (86%) than coronary CT angiography (65%).

Source: HeartFlow Inc., December 1, 2014

Test Identifies Human T-Cell Lymphotropic Virus-I/II

The FDA has approved MP Diagnostics HTLV Blot 2.4 (MP Biomedicals, LLC), a supplemental test for human T-cell lymphotropic virus-I/II (HTLV-I/II).

The product provides an additional, more specific test for human serum or plasma specimens that have previously tested positive on an FDA-licensed HTLV-I/II blood-donor screening test. It is a qualitative enzyme immunoassay intended to confirm infection with HTLV and to differentiate between HTLV-I and HTLV-II.

HTLV is a group of human retroviruses known to cause diseases, such as adult T-cell leukemia/lymphoma and inflammation of the nerves in the spinal cord. Because HTLV can be transmitted through blood, the FDA requires that donated blood be tested for HTLV-I/II antibodies. If the test is positive, the donation is discarded and the donor is notified. The MP Diagnostics HTLV Blot 2.4 allows blood donation sites to confirm the donor’s infection, identify its cause (HTLV-I or HTLV-II), and tell the donor.

Many people who are infected with HTLV do not develop symptoms, signs of infection, or a disease, but they can still transmit the viruses to others.

Source: FDA, December 11, 2014

Warning Would Limit Power Morcellator Use

The FDA has warned against using laparoscopic power morcellators for hysterectomies or myomectomies in most women to help reduce the risk of spreading unsuspected cancer during treatment for uterine fibroids.

The agency recommends that manufacturers add a boxed warning to the devices’ labeling that notes: “Uterine tissue may contain unsuspected cancer. The use of laparoscopic power morcellators during fibroid surgery may spread cancer and decrease the long-term survival of patients. This information should be shared with patients when considering surgery with the use of these devices.”

The FDA also suggested revised labeling stating that use of the devices is contraindicated in these instances:

- The removal of uterine tissue containing suspected fibroids in patients who are peri- or post-menopausal or who are candidates for en bloc tissue removal through the vagina or mini-laparotomy. This comprises the majority of women with fibroids who undergo hysterectomy and myomectomy.
- Gynecological surgery in which the tissue to be morcellated is known or suspected to be cancerous.

The FDA estimates that about one in 350 women who undergo hysterectomy or myomectomy for fibroids is found to have an unsuspected uterine sarcoma.
If laparoscopic power morcellation is performed in these women, there is a risk that the procedure will spread the cancerous tissue within the abdomen and pelvis, significantly worsening the patient’s likelihood of long-term survival.

For a narrow population of patients, laparoscopic power morcellation may be an appropriate option. For example, some younger women who are interested in maintaining their ability to have children or wish to keep their uterus intact after being informed of the risks may be candidates for the procedure.

Source: FDA, November 24, 2014

**Device Recalls**

**Esprit V1000 and V200 Ventilators**

Respironics California Inc. has recalled Esprit V1000 and V200 Ventilators that use its 3rd Generation Power Supply, which may prevent the ventilator from using external electricity or from switching back to external electricity after using battery power. If the battery is missing or depleted, the ventilator will stop working.

The class I recall also covers 3rd Generation Power Supply Repair Part Kits. These devices were distributed from December 21, 2012, to July 9, 2014. Customers will be contacted to arrange replacements. Meanwhile, ventilators can remain in use, but operators should watch for power alerts.

Source: FDA, November 19, 2014

**CONMED AED Electrodes**

Some PadPro and R2 Multi-function Defibrillation Electrodes (CONMED Corporation) will not work with Philips FR3 and FRx automated external defibrillators (AEDs) because of a connector compatibility issue.

The FRx AED unit requires the pads to be preconnected and will issue a continuous alarm chirp to alert the user that the proper pads are not connected. The FR3, however, does not require preconnection, and the user will not discover the incompatibility until the AED must be used, which may delay therapy.

The electrodes were distributed from March 1, 2012, through October 29, 2014. CONMED is revising its labeling to clarify that these 174,610 electrodes are incompatible with Philips FR3 and FRx units. The electrodes do not need to be returned, but the FDA has labeled this a class 1 recall.

All lots of these products are affected:
- Adult Radiotranslucent Electrodes (2516H);
- Pediatric Radiotranslucent Electrodes (2603H); Mini Pediatric Radiotranslucent Electrodes (2602H); Pediatric R2 Multifunction Electrodes (3115-1750); and
- R2 Multifunction Electrodes (3115-1751).

For information, contact CONMED at 727-399-5276, Monday through Friday, 8 a.m. to 5 p.m. Eastern time.

Source: CONMED Corporation, November 26, 2014

**Heart Sync AED Electrodes**

Heart Sync Inc. says some of its multifunction defibrillation electrodes can’t be used with Philips FR3 and FRx automated external defibrillators (AEDs) because of a connector compatibility issue.

The FRx AED unit requires the pads to be preconnected and will issue a continuous alarm chirp to alert the user that the proper pads are not connected. The FR3, however, does not require preconnection, and the user may not discover the incompatibility issue until the AED must be used, potentially delaying therapy.

The electrodes were distributed from October 26, 2011, through November 26, 2014. Heart Sync is revising its labeling to clarify that use of these 113,750 electrodes is incompatible with the Philips FR3 and FRx AED units. The electrodes do not need to be returned.

All lots of these electrodes are affected:
- Adult Radiotransparent Electrodes (C100-PHILIPS, C100AC-PHILIPS, T100LO-PHILIPS); and Radiotranslucent Electrodes (T100-PHILIPS, T100AC-PHILIPS). For information, contact Heart Sync at 734-213-5530, 24 hours a day, seven days a week.

Source: Heart Sync Inc., November 26, 2014

**Gel-E Donut / Squishon 2**

Children’s Medical Ventures (CMV) has recalled 336,695 Gel-E Donut gel pillows and Squishon 2 gel cushions due to potential mold contamination—its second recall of the products, which were distributed between July 2012 and August 2014.

The class I recall affects models 92025-A, -B, and -C and 91033-2. Customers were advised to throw them out even if no mold is visible; they will receive a credit.

In May 2014, CMV (a Philips Healthcare business) initiated a recall due to mold contamination that occurred during manufacturing. Mold raised the possibility of fungal infections that could range from superficial to life-threatening. CMV implemented a process meant to reduce mold on the products prior to shipment.

However, Philips received 12 new complaints of visible mold, with one injury. So the company again recalled the products, which support a hospitalized infant’s head or body. U.S. customers with questions may reach their local Philips representative via 770-510-4681 or 770-510-4684.

Source: Philips Healthcare, November 14, 2014, and FDA, December 2, 2014

**Customed Surgical Convenience Packs**

Customed, Inc., has expanded its June 2014 class I recall of sterile surgical Convenience Kits to a total of 486,555 units. A potential package integrity defect may compromise their sterility, and serious deficiencies in manufacturing and storage may significantly affect the risk of contamination and infection.
No serious injuries or deaths have been reported, but the FDA suspects any infections would probably not be attributed to the kits, which were distributed from November 2011 to October 9, 2014. They are used mainly in hospitals or medical offices for a range of surgical procedures.

A list of affected items and lots is available at http://tinyurl.com/Customed2. Those with questions may reach the Customed recall coordinator at 787-622-5151, extension 7510 or 7540, Monday through Friday, 8 a.m. to 5 p.m. Eastern time.

Source: FDA, November 21, 2014

**Urgent Correction for INRatio**

The INRatio and INRatio2 PT/INR Monitor system (Alere Inc.) may sometimes report an international normalized ratio (INR) that is significantly lower than the result obtained using a reference INR system in the laboratory, according to an “urgent correction” from Alere. The problem can arise if the patient has certain medical conditions or if the instructions in the test’s labeling are not followed.

The products should not be used with patients who have anemia of any type, conditions associated with elevated fibrinogen (including inflammatory conditions, severe infections, advanced cancer, or end-stage renal disease requiring hemodialysis), or any bleeding or unusual bruising. Such patients should immediately be transitioned to a laboratory INR method. Alere recommends that patients have periodic verification of their INR using a laboratory method.

Alere is working on product improvements that will mitigate the potential for discrepant results. Customers with questions can contact Alere at 1-877-929-2579.

Source: Alere Inc., December 8, 2014

**Siemens Gram Negative Tests**

Siemens Healthcare Diagnostics, Inc., is recalling Rapid Gram Negative Combo Panels (including Rapid Neg BP Combo Panel Type 3 and Rapid Neg Urine Combo Panel Type 1) that may report some bacteria are sensitive to certain antibiotics when the bacteria are actually resistant. The products are meant to identify Enterobacteriaceae, Acinetobacter, and *Pseudomonas aeruginosa* and measure how they will respond to aztreonam, cefotaxime, ceftazidime, and ceftriaxone.

Details about this class I recall (including product and lot numbers) are available at http://tinyurl.com/SiemensPanels. Customers should discard the devices; assistance is available via the Siemens Customer Care Center at 1-800-988-2477, 24 hours a day, seven days a week.

Source: FDA, December 2, 2014

**Baxter Intravia Containers**

Baxter International Inc. recalled two lots of empty plastic Intravia containers with PVC ports and a sterile fluid path after receiving complaints about particulate matter found in the fluid path. The class I recall covers containers with capacities of 150 mL (lot UR13D15112, distributed from April to June 2013) and 500 mL (lot UR13K14095, distributed from November 2013 to March 2014). Call Baxter with questions at 1-800-422-9837, Monday through Friday, 8 a.m. to 5 p.m. Central time.

Source: FDA, November 20, 2014

**DEVICE SPOTLIGHT**

**Kunj Gohil, PharmD, RPh**

**Name:** VEPTR and VEPTR II Vertically Expandable Prosthetic Titanium Rib Devices

**Manufacturer:** DePuy Synthes Spine (Johnson & Johnson), Raynham, Massachusetts

**Approval Date:** December 8, 2014

**Purpose:** The VEPTR/VEPTR II devices are indicated for the treatment of thoracic insufficiency syndrome (TIS) in pediatric patients.

**Description:** The VEPTR device is a metal rod designed with a precise curve and attached to the ribs on either side of the spine. Hooks located at either end of the device anchor it to the patient’s body. The device must be surgically implanted and adjusted to fit the patient, and subsequent procedures may be necessary to correct any existing deformities.

**Benefit:** This tool is designed to help straighten the spinal column and separate the ribs, allowing the lungs to grow and fill with air. The VEPTR will be lengthened or replaced at certain times during a patient’s development to allow for proper lung growth and management of spinal or chest wall deformity. The long-term effects of this treatment will be seen through an expanded life span, decreased dependence on oxygen therapy, and increased physical ability. The new FDA clearance is expected to improve access to the devices, which were previously available under a humanitarian device exemption.

**Sources:** www.fiercemedicaldevices.com, www.fda.gov

**Name:** Animas Vibe

**Manufacturer:** Animas Corporation (Johnson & Johnson), Chesterbrook, Pennsylvania

**Approval Date:** November 25, 2014

**Purpose:** The Animas Vibe System, a combination insulin pump and continuous glucose monitor (CGM), is indicated for the management of type-1 diabetes.

**Description:** The Animas Vibe System integrates an advanced CGM technology, the Dexcom G4 Platinum sensor, with a precise insulin pump. The sophisticated CGM technology reads a patient’s glucose levels every five minutes, which can guide patients in meeting their insulin requirements.

**Benefit:** Patients with type-1 diabetes are plagued by frequent glucose monitoring needs and explicit insulin require-
ments. Aside from the burden this disease puts on a patient’s health, it also poses a major inconvenience for their day-to-day activities. The Animas Vibe System is designed to simulate the actions of a natural pancreas by monitoring glucose levels frequently and providing insulin at varying increments. Users also have the ability to personalize dosing to meet their individual insulin-to-carbohydrate ratios, insulin sensitivity, and blood glucose targets.

Sources: www.fiercemedicaldevices.com, www.animas.com

Name: Radius-7 with the Root patient monitoring and connectivity platform

Manufacturer: Masimo, Irvine, California

Approval Date: December 1, 2014

Purpose: The Radius-7 is approved to track patient oxygen saturation, pulse rate, and acoustic respiration rate in an ambulatory or home care setting.

Description: The Radius-7 is a wearable patient monitoring device that can wirelessly communicate with Root, Masimo’s patient monitoring and connectivity software that links a variety of devices regardless of company origin. Application of the Radius-7 is extremely simple, since the device attaches to the arm with an armband.

Benefit: The ability of this device to wirelessly communicate patient-specific data will increase patients’ mobility while ensuring that they are continuously monitored. Not only will the device reduce the need for nursing assistance, but it will also allow physicians to be notified if a critical change occurs in a patient’s oxygen saturation, pulse rate, and/or respiration rate.

Sources: www.fiercemedicaldevices.com, http://ir.masimo.com