NEW DRUG APPROVALS
Corlanor for Heart Failure

Ivabradine (Corlanor, Amgen) has received FDA approval to reduce the risk of hospitalization for worsening heart failure (HF). The medication is indicated in patients with stable, symptomatic chronic HF who have a left ventricular ejection fraction (LVEF) of 35% or less, are in sinus rhythm with a resting heart rate of at least 70 beats per minute (BPM), and are receiving maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use.

Ivabradine blocks the hyperpolarization-activated cyclic nucleotide-gated channel responsible for the cardiac pacemaker, which regulates heart rate. Taken orally, the medication reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the If current to slow the heart rate with no effects on ventricular repolarization or myocardial contractility.

The randomized, double-blind, placebo-controlled, phase 3 Systolic Heart Failure Treatment With the If Inhibitor Ivabradine Trial (SHIFT) compared ivabradine with placebo on top of standard-of-care (SOC) therapies, including beta blockers, in more than 6,500 clinically stable patients in sinus rhythm with an LVEF of 35% or less, a resting heart rate of 70 BPM or more, and a hospitalization for HF within the past 12 months. Patients received SOC including beta blockers (89%), angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers (91%), diuretics (83%), and anti-aldosterone agents (60%).

Compared with placebo, ivabradine resulted in a 26% relative risk reduction for hospitalization for worsening heart failure; there was no favorable effect on cardiovascular death for worsening HF. The most common adverse events with ivabradine compared with placebo included bradycardia, hypertension, increased blood pressure, atrial fibrillation, and luminous phenomena or visual brightness.

Source: Amgen, April 16, 2015

Cholbam for Bile Disorders

The FDA has made cholic acid capsules (Cholbam, Asklepios Pharmaceuticals) its first approved treatment for children and adults with bile acid synthesis disorders due to single enzyme defects and for peroxisomal disorders (including Zellweger spectrum disorders).

Patients with these rare genetic metabolic conditions lack the enzymes needed to synthesize cholic acid, a primary bile acid produced in the liver from cholesterol. This leads to reduced bile flow, cholestasis, and the malabsorption of fats and fat-soluble vitamins in the diet. Untreated patients fail to grow and can develop life-threatening liver injuries.

Cholbam is approved as an oral treatment for people 3 weeks of age and older. Cholic acid's efficacy in treating bile acid synthesis disorders due to single enzyme defects was assessed in an uncontrolled trial involving 50 patients during an 18-year period. An extension trial followed 21 of these patients and enrolled 12 more; interim efficacy data from this study were available for an additional 21 months. On average, patients were 4 years of age at the start of cholic acid treatment. Responses (improvements in baseline liver-function tests and weight) were observed in 64% of patients with evaluable data. Two-thirds of the patients survived longer than three years.

Cholic acid's efficacy in treating peroxisomal disorders, including Zellweger spectrum disorders, was assessed in an uncontrolled trial involving 29 patients during an 18-year period. An extension trial followed 10 of these patients and enrolled two more; interim efficacy data from this study were available for an additional 21 months. Most patients were younger than 2 years of age at the start of cholic acid treatment. Responses (improvements in baseline liver-function tests and weight) were observed in 46% of patients with evaluable data, and 42% of patients survived longer than three years.

Diarrhea was the most common adverse event. Use of the medication should be monitored carefully by an experienced hepatologist or pediatric gastroenterologist; treatment should be discontinued in patients with worsening liver function. Cholbam does not affect other manifestations of bile acid disorders due to single enzyme defects or peroxisomal disorders. The FDA is requiring a post-approval observational study of Cholbam’s long-term safety.

Source: FDA, March 17, 2015

Anthrasisl for Anthrax

The FDA has approved anthrax immune globulin intravenous (human) (Anthrasisl, Cangene Corporation) to treat inhalational anthrax in combination with antibacterial drugs.

Inhalational anthrax can occur after exposure to infected animals or contaminated animal products or as a result of an intentional release of anthrax spores. It is caused by breathing in the spores of the bacterium *Bacillus anthracis*, which replicates in the body and produces toxins that can cause massive injury and death.

To help prepare the nation against a possible anthrax attack, the U.S. Department of Health and Human Services’ Biomedical Advanced Research and Development Authority purchased Anthrasil under Project BioShield in 2011 as an experimental drug for the U.S. Strategic National Stockpile, which will store the product. Prior to the FDA’s approval, use of the drug would have required an FDA emergency use authorization.

Anthrasisl is made from the plasma of people vaccinated against anthrax. The plasma contains antibodies that neutralize
toxins produced by the anthrax bacteria. Anthrasil’s efficacy was studied in animals because it was not feasible or ethical to conduct adequately controlled studies in humans. Rabbits and monkeys were exposed to a lethal aerosolized dose of B. anthracis spores, then treated with Anthrasil or a placebo. Survival in anthrax-infected monkeys treated with Anthrasil ranged from 36% to 70% compared to 0% in the placebo group, with a trend toward increased survival at higher doses. Rabbits treated with a moderate dose of Anthrasil after infection exhibited 26% survival compared to 2% survival in the placebo group. Another study in rabbits showed that combining Anthrasil and antibiotics resulted in 71% survival compared to 25% survival in animals treated with antibiotics alone.

The product’s safety was tested in 74 healthy human volunteers. The most commonly observed side effects were headache, back pain, nausea, and infusion-site pain and swelling.

Source: FDA, March 25, 2015

**Generic Approvals**

**Glatiramer Acetate Injection**

Sandoz has received FDA approval to market glatiramer acetate injection 20 mg/mL daily injection—the first generic version of Copaxone (Teva Pharmaceutical Industries), which is indicated to treat relapsing forms of multiple sclerosis. The generic was developed in partnership by Sandoz and Momenta Pharmaceuticals, which said Sandoz is evaluating launch timing. The drug will be marketed under the name Glatopa and be fully substitutable at the pharmacy level.

Copaxone generated $3.6 billion in U.S. sales for Teva in 2013, according to IMS Health. The medication has been the subject of a protracted fight in the courts and at the FDA over Teva’s patent and other issues, and that fight is not over. The U.S. Supreme Court sent the case back to a lower court earlier this year. Meanwhile, Teva is converting patients to a new long-acting version of the drug.

Sources: FDA, Momenta Pharmaceuticals, and FiercePharma, April 16, 2015, and IMS Health

**Tenofovir Disoproxil Fumarate**

The FDA has approved the sale of 300-mg tenofovir disoproxil fumarate tablets by Teva Pharmaceuticals USA—the first generic version of Viread (Gilead Sciences).

Viread is a nucleotide analog human immunodeficiency virus-1 reverse transcriptase inhibitor and a hepatitis B virus reverse transcriptase inhibitor. It is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 2 years of age and older. It is also indicated for the treatment of chronic hepatitis B in patients 12 years of age and older. Viread has boxed warnings for lactic acidosis and severe hepatomegaly with steatosis and for post-treatment exacerbation of hepatitis.

Sources: FDA, March 18, 2015, and Viread prescribing information

**Levoleucovorin Calcium Injection**

The FDA has approved levoleucovorin calcium injection, 10 mg (base)/mL (Sandoz), the first generic version of Fusilev Injection (Spectrum Pharmaceuticals, Inc.). Fusilev is a folate analog indicated for rescue after high-dose methotrexate therapy in osteosarcoma; it is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.

Sources: FDA, March 9, 2015, and Fusilev Injection prescribing information

**Darifenacin Hydrobromide ER**

Anchen Pharmaceuticals, Inc., has received FDA approval to market darifenacin hydrobromide extended-release tablets, 7.5 mg and 15 mg, the first generic version of Enablex Extended-Release Tablets (Warner Chilcott LLC). Enablex is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Sources: FDA, March 13, 2015, and Enablex prescribing information

**NEW INDICATIONS**

**Saphris for Children’s Bipolar I**

The FDA has approved asenapine (Saphris, Actavis) as monotherapy for the acute treatment of manic or mixed episodes associated with bipolar I disorder in patients 10 to 17 years of age. Saphris is the only atypical antipsychotic treatment with a sublingual formulation.

Asenapine, initially approved in 2009, is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults as monotherapy or as adjunctive therapy with lithium or valproate, and for the acute and maintenance treatment of schizophrenia in adults.

The latest approval was based on a three-week monotherapy trial in 302 patients 10 to 17 years of age who received asenapine twice daily in doses of 2.5 mg, 5 mg, or 10 mg. Asenapine was shown to improve the Young Mania Rating Scale (YMRS) total score and the Clinical Global Impression–Bipolar (CGI-BP) severity of illness overall score compared with placebo.

The most common adverse events associated with asenapine include sleepiness, dizziness, strange sense of taste, numbing of the mouth, nausea, increased appetite, feeling tired, and weight gain.

Asenapine will be available for pediatric patients with bipolar I disorder in 2.5-mg, 5-mg, and 10-mg black cherry-flavored sublingual tablets.

Source: Actavis, March 13, 2015
Kalydeco for Younger Children

The FDA has approved ivacaftor (Kalydeco, Vertex Pharmaceuticals) for use in children ages 2 to 5 years with cystic fibrosis (CF) who have one of 10 mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, and R117H). Ivacaftor was previously indicated in the U.S. for CF patients 6 years of age and older with these mutations.

Approximately 300 U.S. children ages 2 to 5 years have one of these 10 mutations, which result in a gating defect in the CFTR protein. A new weight-based oral granule formulation of ivacaftor (50 mg and 75 mg) that can be mixed in soft foods or liquids was created to meet the needs of children in this age group who may be unable to swallow a tablet.

The new approval was based on results from an open-label, phase 3, 24-week study that was designed to evaluate the safety and pharmacokinetics of weight-based dosing of ivacaftor (50 mg or 75 mg twice daily) in children ages 2 to 5 years.

Source: Vertex Pharmaceuticals, March 18, 2015

Eylea for Retinopathy in DME

The FDA has expanded the approved uses of aflibercept injection (Eylea, Regeneron Pharmaceuticals) to include the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME).

A physician injects aflibercept into the eye once a month for the first five injections and then once every two months. It is intended to accompany appropriate interventions to control blood sugar, blood pressure, and cholesterol.

The safety and efficacy of aflibercept in DR in patients with DME were evaluated in 679 participants in two clinical studies. Participants were randomly assigned to receive aflibercept or macular laser photoacoagulation (use of a laser to burn small areas of the retina). At week 100, patients treated with aflibercept showed significant improvement in the severity of their DR compared with patients who did not receive aflibercept.

The most common adverse effects associated with aflibercept included bleeding of the conjunctiva, eye pain, cataracts, “floaters,” increased intraocular pressure, and vitreous detachment. Serious adverse reactions included endophthalmitis and retinal detachments.

The FDA designated aflibercept a breakthrough therapy for the new indication and evaluated it under the priority review program. The FDA previously approved aflibercept to treat neovascular age-related macular degeneration and to treat DME and macular edema secondary to retinal-vein occlusions.

Source: FDA, March 25, 2015

NEW FORMULATIONS
Combined DTaP/Polio Vaccine

The FDA has approved a vaccine that combines immunization against diphtheria, tetanus, and pertussis with immunization against poliomyelitis. Diphtheria and tetanus toxoids and acellular pertussis absorbed plus inactivated poliovirus vaccine (Quadracel, Sanofi Pasteur) is intended for children 4 to 6 years of age.

The Centers for Disease Control and Prevention recommends children in this age group receive their fifth dose of the diphtheria, tetanus and acellular pertussis (DTaP) vaccine series and their fourth dose of the inactivated poliovirus (IPV) vaccine series. Quadracel can be administered as a fifth dose in the DTaP series and as a fourth or fifth dose in the IPV series.

A pivotal multicenter, randomized, controlled, phase 3 study compared the safety and immunogenicity of Quadracel vaccine (DTaP-IPV) with DTaP (Daptacel, Sanofi) and IPV (Ipol, Sanofi) vaccines in children 4 through 6 years of age who were previously vaccinated with Daptacel and/or DTaP/IPV/Hib (Pentacel, Sanofi). Quadracel’s safety and immunogenicity profiles were found to be similar to those of separately administered Daptacel and Ipol. Side effects of Quadracel may include pain, redness, and swelling at the injection site; muscle pain; fatigue; and headache. There is a small risk of allergic reactions.

Source: Sanofi Pasteur, March 25, 2015

Jadenu for Iron Chelation

The FDA has approved deferasirox tablets (Jadenu, Novartis), a new oral formulation of deferasirox tablets for oral suspension (Exjade, Novartis) for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older and chronic iron overload in non–transfusion-dependent thalassemia syndromes in patients 10 years of age and older.

Many patients with sickle cell disease, thalassemia, or myelodysplastic syndromes need repeated blood transfusions and, consequently, long-term daily chelation therapy. Jadenu oral tablets can be taken in a single step, with or without a light meal, simplifying administration of treatment for chronic iron overload. Exjade must be mixed in liquid and taken on an empty stomach.

Jadenu received accelerated approval based on a reduction of liver iron concentrations and serum ferritin levels. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

Jadenu carries a boxed warning noting that it may cause serious and fatal renal toxicity, including failure; hepatic toxicity, including failure; and gastrointestinal hemorrhage. Jadenu therapy requires close patient monitoring, including laboratory tests of renal and hepatic function.

Sources: Novartis, March 30, 2015, and Jadenu prescribing information
DRUG NEWS
HCV Drug Combination Linked With Bradycardia
Severe or life-threatening bradycardia can occur in patients who take Gilead Sciences’ hepatitis C drugs sofosbuvir (Sovaldi) or ledipasvir/sofosbuvir (Harvoni) in combination with the antiarrhythmic drug amiodarone and another direct-acting antiviral for the treatment of hepatitis C infection, the FDA warns.

Symptomatic bradycardia has been reported in nine patients taking the drug combination; one died from cardiac arrest and three needed pacemakers to regulate their heart rhythms. The reasons remain unknown and under investigation. The patients had underlying cardiac disease, concomitant beta-blocker therapy, and/or advanced liver disease. In general, symptoms occurred shortly after they starting taking Harvoni or Sovaldi with other direct-acting antivirals and amiodarone; resolved when they stopped taking the combination; and reoccurred if they started taking the drugs again.

The FDA is adding information about bradycardia (a serious slowing of the heart rate) to the Harvoni and Sovaldi labels. The agency recommends that health care professionals not prescribe either product with amiodarone and another direct-acting antiviral, such as simeprevir (Olysio, Johnson & Johnson) or investigational daclatasvir (Bristol-Myers Squibb). However, if alternative treatment options are unavailable, the agency recommends heart monitoring in an inpatient hospital setting for the first 48 hours, followed by monitoring in a doctor’s office or self-monitoring of the heart rate every day for at least the first two weeks of treatment.

Source: FDA, March 24, 2015

Boxed Warning for Feraheme
The FDA added a boxed warning to the anemia drug ferumoxytol (Feraheme, AMAG Pharmaceuticals) after serious allergic reactions were linked with 18 deaths in five years. The agency also strengthened an existing warning about the possibility of allergic reactions, changed the prescribing instructions, and added a new contraindication: a strong recommendation against using ferumoxytol in patients who have had an allergic reaction to any intravenous (IV) iron replacement product such as ferumoxytol.

Ferumoxytol is specifically approved only to treat iron-deficiency anemia in patients with chronic kidney disease (CKD). It is given as an IV infusion by health care professionals in a hospital, outpatient clinic, or medical office. Like other IV iron products, ferumoxytol may only be given where emergency personnel and equipment are immediately available to treat potentially life-threatening allergic reactions.

A search of the FDA Adverse Event Reporting System database identified 79 cases of anaphylactic reactions associated with Feraheme administration from June 30, 2009 (when the drug was approved) to June 30, 2014. Eighteen cases were fatal despite immediate medical intervention and emergency resuscitation attempts. The 79 patients ranged in age from 19 to 96 years. Nearly half of the reactions occurred with the first dose of Feraheme. Frequently reported symptoms included cardiac arrest, hypotension, dyspnea, nausea, vomiting, and flushing. Of the 79 cases, 43% of the patients had a medical history of drug allergies.

Source: FDA, March 30, 2015

Olanzapine Study Inconclusive
The FDA declined to recommend changes to the prescribing or use of olanzapine pamoate injection (Zyprexa Relprevv, Eli Lilly) after reviewing the inconclusive results of a study that sought to explain elevated levels of the drug in two patients who died.

The FDA is unable to exclude the possibility that the deaths were caused by rapid but delayed entry of the drug into the bloodstream after intramuscular injection. The study suggested that much of the increase in drug levels could have occurred after death, which could explain the extremely high blood levels found in the two patients who died three to four days after receiving injections of appropriate doses of olanzapine pamoate.

The labeling for olanzapine pamoate includes a boxed warning regarding the potential for post-injection delirium sedation (PDSS). The FDA recommends that patients read the medication guide that comes with the olanzapine pamoate prescription each time they are about to receive an injection, as information may have been added. Patients receiving olanzapine pamoate or their caregivers should immediately report symptoms of PDSS to a health care professional.

Health care professionals should continue to follow the requirements of the olanzapine pamoate risk evaluation and mitigation strategy (REMS) and current label recommendations. Key REMS requirements include the following: for a patient to receive treatment, the prescriber, health care facility, patient, and pharmacy must all be enrolled in the olanzapine pamoate patient-care program; injections must be administered at a REMS-certified health care facility with ready access to emergency response services; patients must be continuously monitored at the REMS-certified health care facility for at least three hours after an injection; and patients must be accompanied afterward to their destination.

Source: FDA, March 23, 2015, and June 18, 2013

HCV Costs Medicare Billions
Medicare spent $4.5 billion in 2014 on costly new medications that cure hepatitis C—more than 15 times what it spent in
2013 on older treatments for the disease, according to federal data reported by the Washington Post. The outlays will be borne largely by taxpayers but will also raise deductibles and out-of-pocket costs for many of Medicare’s 39 million enrollees.

Medicare Part D spent approximately $286 million on earlier-generation drugs for the hepatitis C virus (HCV) in 2013. Sofosbuvir (Sovaldi, Gilead Sciences), which costs $84,000 for a 12-week course of treatment, accounted for more than $3 billion of the 2014 spending. Spending on ledipasvir/sofosbuvir (Harvoni, Gilead) hit $670 million even though it came on the market in October 2014. Simeprevir (Olysio, Janssen), which is often taken in conjunction with Sovaldi, costs $821 million. Medicare also spent $157 million on older HCV drugs in 2014, bringing total spending for the category to more than $4.7 billion.

The spending surge is unlike anything ever seen by Part D, which has benefited in recent years from a slowdown in prescription drug costs as blockbuster medications lost patent protection. Expensive specialty medications threaten to drastically increase the price of Part D, which cost the federal government $65 billion in 2013 (not including patients’ monthly premiums).

It generally takes the government more than a year to compile data on drug spending, but the Centers for Medicare and Medicaid Services provided the data on HCV drugs to ProPublica in response to a Freedom of Information Act request and follow-up inquiries. In preliminary data, state Medicaid programs collectively spent $1.2 billion on HCV drugs in the first nine months of 2014. Many Medicaid programs and private insurers took a more restrictive approach toward the drugs than Medicare did.


**Breakthrough Therapy Status**

**Rucaparib for Ovarian Cancer**

The FDA has designated rucaparib (Clovis Oncology) a breakthrough therapy for advanced ovarian cancer in patients who have received at least two lines of platinum-containing therapy and who have BRCA-mutated tumors, including germline and somatic BRCA mutations.

Rucaparib is an oral inhibitor of poly(ADP-ribose) polymerase 1 (PARP1) and PARP2 being developed for the treatment of platinum-sensitive ovarian cancer, specifically in patients with tumors with BRCA mutations and other DNA repair deficiencies beyond BRCA, commonly referred to as being “BRCA-like” or having “BRCAness.”

The breakthrough therapy designation was based on interim efficacy and safety results from two ongoing phase 2 studies in ovarian cancer patients, including the ARIEL2 trial. Data from ARIEL2 showed that 16 of 23 evaluable BRCA-mutant patients (70%) achieved a Response Evaluation Criteria in Solid Tumors (RECIST) and/or cancer antigen 125 response. Responses were observed in both germline and somatic BRCA-mutant tumors. The data also demonstrated that rucaparib was well tolerated.

Source: Clovis Oncology, April 6, 2015

**Viaskin Peanut Allergy Treatment**

DBV Technologies has received the FDA’s breakthrough therapy designation for Viaskin Peanut, a treatment for peanut allergies in children, and is preparing for phase 3 trial.

A phase 2b trial, Viaskin Peanut Efficacy and Safety (VIPES), showed a positive response for Viaskin Peanut 250 mcg in children and adults. The product (which received an FDA fast-track designation in 2011) has an excellent safety profile, the company says.

The Viaskin technology platform delivers biologically active compounds, including allergens, onto the superficial layers of intact skin using an electrostatic patch. This activates the immune system by specifically targeting antigen-presenting cells without allowing passage of the antigen into the bloodstream.

Source: DBV Technologies, April 9, 2015

**Priority Review**

**Kyprolis for Relapsed Multiple Myeloma**

The FDA has granted priority review to a supplemental new drug application for carfilzomib injection (Kyprolis, Onyx Pharmaceuticals/Amgen) for the treatment of patients with relapsed multiple myeloma (MM) who have received at least one prior therapy. The application is designed to support the conversion of accelerated approval to full approval and to expand the Kyprolis indication; the target action date is July 26, 2015.

The application includes data from the phase 3 ASPIRE trial. ASPIRE evaluated carfilzomib in combination with lenalidomide and low-dose dexamethasone, compared with lenalidomide and low-dose dexamethasone alone, in 792 patients with relapsed MM after treatment with one to three prior regimens.

Progression-free survival improved significantly with carfilzomib compared with the control group (median: 26.3 months versus 17.6 months, respectively). The Kaplan–Meier 24-month overall survival rates were 73.3% and 65.0% in the carfilzomib and control groups, respectively.

In July 2012, the FDA granted accelerated approval to Kyprolis for the treatment of MM patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval was based on the response rate. The clinical benefit of Kyprolis, such as an improvement in survival or symptoms, has not been verified in these patients.
Sources: Amgen, March 30, 2015, and New England Journal of Medicine, January 8, 2015

**Lifitegrast for Dry Eyes**

The FDA is giving priority review to lifitegrast (Shire PLC), an investigational treatment for dry eye disease in adults. A decision is expected in October 2015 on the application, which is supported by four clinical trials involving more than 1,800 patients.

Lifitegrast, a novel small-molecule integrin inhibitor, binds to the integrin LFA-1 (lymphocyte function-associated antigen-1), a cell surface protein found on leukocytes, and blocks the interaction of LFA-1 with its cognate ligand ICAM-1 (intercellular adhesion molecule-1). ICAM-1 is overexpressed in corneal and conjunctival tissues in dry eye disease. LFA-1/ICAM-1 interaction contributes to the formation of immunological synapses resulting in T-cell activation and migration to target tissues.

Source: Shire PLC, April 9, 2015

**Orphan Drug Designations**

**Sanguinate for Sickle Cell Disease**

The FDA has granted an orphan drug designation to Sanguinate (Prolong Pharmaceuticals, LLC) for the treatment of sickle cell disease (SCD).

Prolong is studying Sanguinate’s safety and efficacy in SCD and other diseases caused by the effects of oxygen deprivation. Through its antivasoconstrictive properties, Sanguinate facilitates the transfer of oxygen to oxygen-deprived cells and tissues. Many of SCD’s comorbidities are caused by a spiraling cycle of sickling, hemolysis, and blood vessel inflammation. By correcting oxygen levels and downregulating inflammation, Sanguinate can potentially treat many of these comorbidities. Phase 2 trials are planned for vasoocclusive crisis and leg ulcers secondary to SCD.

Source: Prolong Pharmaceuticals, LLC, April 8, 2015

**SPI-026 for Pulmonary Arterial Hypertension**

SPI-026 (tacrolimus, Selten Pharma, Inc.) has received an FDA orphan drug designation for the treatment of pulmonary arterial hypertension (PAH). Results of a proof-of-concept, safety, and tolerability study have been “very encouraging,” says the company, which is about to begin a phase 2b clinical trial.

SPI-026 is an investigational bone morphogenetic protein receptor type II (BMPR2) pathway activator discovered by and being developed with Stanford University researchers. It prevented the development of PAH in mice with a deletion of BMPR2 endothelial cells in a chronic hypoxia model, and reversed PAH and neointimal/occlusion in the lungs in rats with neointima formation following vascular endothelial growth factor receptor blockade and chronic hypoxia. It has been shown to be safe and tolerable in patients with PAH.

Source: Selten Pharma, Inc., March 18, 2015

**CRS-207 for Mesothelioma**

CRS-207 (Aduro Biotech, Inc.) has received an FDA orphan drug designation for the treatment of mesothelioma. The FDA previously gave CRS-207 an orphan designation for the treatment of pancreatic cancer.

Aduro is developing CRS-207 for patients with malignant pleural mesothelioma who have not received prior therapy and are not eligible for surgical resection. Patients are being enrolled in a single-arm phase 1b clinical trial of CRS-207 in combination with standard-of-care chemotherapy. Interim results presented at the International Mesothelioma Interest Group Conference in October 2014 demonstrated a 94% rate of disease control (12 partial responses and three cases of stable disease) for the 16 treated, evaluable patients with response data. At the time, estimated progression-free survival was 7.5 months.

CRS-207 is based on Aduro’s live-attenuated, double-deleted Listeria monocytogenes immunotherapy platform that induces a potent innate and T-cell-mediated adaptive immune response. CRS-207 has been engineered to express the tumor-associated antigen mesothelin.

Source: Aduro Biotech, Inc., March 26, 2015

**Clanotech After Glaucoma Surgery**

CLT-288643 (Clanotech AB) has received the FDA’s orphan drug designation for use as adjuvant treatment to surgery in glaucoma patients. CLT-288643, an α5β1-integrin antagonist, has anti-angiogenic, anti-fibrotic, and anti-inflammatory properties. Based on promising preclinical data in animal models for glaucoma, CLT-288643 has the potential to regulate wound-healing processes following glaucoma surgery.

Source: Karolinska Development AB, March 27, 2015

**Medication Recalls**

**North Carolina Pharmacy Shut Down**

The FDA is urging health care professionals and patients not to use products made and distributed by the Prescription Center pharmacy in Fayetteville, North Carolina. The North Carolina Board of Pharmacy closed the company and ordered a recall of all sterile and non-sterile products it compounded, repackaged, or distributed between September 10, 2014, and March 10, 2015.

In a March inspection, state inspectors observed “significant deficiencies that raise concerns about the company’s ability to assure the sterility, stability and potency of the sterile and nonsterile human and veterinary drug products that
it produced,” the FDA reported. Products made by the Prescription Center have been distributed nationwide and to Canada. The FDA is not aware of any adverse events associated with the products.

Source: FDA, April 2, 2015

**Baxter IV Solutions**

Baxter International Inc. has recalled 15 lots of intravenous solutions due to the potential presence of particulate matter (identified as material from a solution transmission system pump). The recall involves 0.9% sodium chloride injection, USP, 10% dextrose injection, USP, and lactated ringer’s injection, USP, all 250 mL. The lots were distributed between January 14 and March 5, 2015; a list is available at [http://tinyurl.com/BaxterIVrecall](http://tinyurl.com/BaxterIVrecall). Consumers with questions can call Baxter at 1-800-422-9837, Monday through Friday, 8 a.m. to 5 p.m. Central time.

Source: Baxter International Inc., April 9, 2015

**RESEARCH BRIEFS**

**Is Tau the Key to Alzheimer’s?**

The progression of dysfunctional tau protein drives the cognitive decline and memory loss of Alzheimer’s disease (AD), Mayo Clinic researchers write in *Brain*. Amyloid, the other toxic protein that characterizes AD, builds up as dementia worsens but is not the primary culprit, they say. Mayo researchers in Florida and Minnesota examined amyloid brain scans of older individuals who have not experienced cognitive decline. In the brains of some participants had amyloid visible at pathology. The brains of some participants had amyloid visible at pathology that did not reach the threshold for what would be found in AD brain scans. This is important because amyloid can be found in the brains of older individuals who have not experienced cognitive decline.

Source: Mayo Clinic, March 23, 2015

**Poliovirus Used to Fight Cancer**

Results of a phase 1 clinical trial using a genetically engineered poliovirus to fight recurrent glioblastoma have been “very encouraging,” Duke University researchers say. PVS-RIPO is being investigated as an anticancer agent at Duke’s Preston Robert Tisch Brain Tumor Center, where researchers replaced polioviruses’ inherent disease-causing ability with a piece of genetic code from a rhinovirus. Two patients in the phase 1 trial have been declared cancer-free three years after treatment for glioblastoma that had returned after treatment or surgery—a condition with an expected survival of about nine months. To date, 11 of 22 patients who have undergone the therapy have died. Duke plans to extend the studies into phase 2 and 3 in a quest to establish PVS-RIPO as a possible therapy for brain tumors. In addition, PVS-RIPO has the potential to work for other types of cancers.

PVS-RIPO naturally infects almost all cancer cells because the receptor for poliovirus (which is used for cell entry) is present on most tumor cells. PVS-RIPO kills cancer cells, but not normal cells, because its ability to grow (and kill) depends on biochemical abnormalities present only in cancer cells. Safety testing in nonhuman primates and humans has shown no nerve-cell killing, no ability to cause poliomyelitis, and no ability of PVS-RIPO to change back to wild-type poliovirus that can cause poliomyelitis.

PVS-RIPO is infused directly into a patient’s tumor to deliver the maximal amount of virus to the target. The likely key to PVS-RIPO therapy is its ability to activate patients’ immune response against cancer. Duke’s results were featured in two 60 Minutes segments that detailed the stories of the trial’s 22 patients.

Sources: *Duke Chronicle*, April 3, 2015, and Preston Robert Tisch Brain Tumor Center
Pain Control in Labor Compared

Epidural analgesia is the standard relief for labor pain, but some studies suggest that patient-controlled remifentanil might be a good alternative. Remifentanil (Ultiva, Mylan) is a potent mu-opioid receptor agonist with a short half-life and short elimination half-time, making it suitable for patient control. The drug is rapidly metabolized and redistributed by the fetus.

To learn which type of analgesia women in labor prefer, Dutch researchers conducted a multicenter trial in the Dutch consortium for women’s health and reproductivity. They randomly assigned 709 women to patient-controlled remifentanil and 705 to epidural analgesia. During labor, 447 (65%) of the remifentanil group received analgesia, compared with 347 (52%) of the epidural analgesia group. Of 402 women who received immediate remifentanil, 53 converted to epidural analgesia because of insufficient pain relief.

Women in the remifentanil group had significantly lower overall satisfaction scores than those in the epidural group (6.8 versus 7.3). Mean satisfaction scores were also significantly lower in the remifentanil group for the total period of active labor (5.1 versus 5.9) and after the start of pain relief (5.3 versus 7.0). Epidural analgesia scored highest on pain relief and lowest on pain intensity after pain relief.

Source: BMJ, February 23, 2015

Ketamine Helps Depression

Ketamine is an effective and acceptable treatment for major depressive disorder (MDD) and to a lesser extent bipolar disorder (BD), according to a meta-analysis by researchers from the University of British Columbia, McGill University, and the University of Minnesota.

The researchers looked at eight randomized clinical trials involving 183 patients that compared ketamine (seven using intravenous [IV] ketamine and one using intranasal ketamine) with saline or midazolam. Their analyses suggest that IV or intranasal ketamine led to rapid and persistent clinical remission and response for up to seven days following a single dose. At 24 hours, three days, and seven days, they observed significantly higher rates of clinical remission and response relative to comparators. While effective in both MDD and BD, the drug appeared to be less effective in BD.

On the whole, ketamine was well tolerated. Ketamine infusions were associated with psychotomimetic side effects, but some evidence suggested they may have been related to ketamine’s antidepressant effectiveness. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist; the researchers cite other “positive” research exploring NMDA antagonists without the psychotomimetic effects. No patients had persistent psychosis or affective switches.

Early clinical adoption of ketamine as a treatment for depression will be more likely in areas of medicine “undeterred by the potential for early relapse and where the potential for misuse is negligible,” the researchers say.

Source: Psychological Medicine, March 2015

What Works for Back Pain?

Despite its expense, long-term multidisciplinary rehabilitation may be cost-effective for treating chronic low back pain, according to a team of Australian, Dutch, and Canadian researchers. After analyzing 41 trials comparing biopsychosocial interventions with usual care and physical treatment, the researchers found benefits in reduced pain and disability that lasted beyond one year.

In addition to a physical component, “multidisciplinary” approaches included a psychological component, a social/work-targeted component, or both. Interventions varied in intensity, approach, and setting (inpatient or outpatient). The control interventions were classified as usual care, physical treatment, surgery, and waiting list.

The researchers found moderate-quality evidence that multidisciplinary rehabilitation programs are more effective than usual care and physical treatments for reducing pain and disability from chronic low back pain. They found no difference between the effects of surgery versus multidisciplinary treatment on pain, disability, and work, but they noted that surgery entails a greater risk of adverse events. Patients who received multidisciplinary rehabilitation rather than physical treatment alone were roughly twice as likely to be back at work in a year.

The “modest” results should be weighed against the monetary and time commitments associated with multidisciplinary rehabilitation, the researchers caution. They suggest referring only those patients for whom low back pain has major physical and psychological effects.

Source: BMJ, February 18, 2015

Gauging Veterans’ Suicide Risk

Posttraumatic stress disorder (PTSD), traumatic brain injury (TBI), and chronic pain have affected so many veterans that they’ve been grouped into a polytrauma clinical triad (PCT). Together and alone, they’ve been linked to an increased risk of suicide.

Researchers from Texas, Massachusetts, and Utah designed a study to see whether PTSD, TBI, and pain are more strongly associated with suicide among veterans of Iraq and Afghanistan in certain combinations, and how they compare as risk indicators with other disorders, such as depression and substance abuse.

In the retrospective study of 211,652 veterans, 5,653 (2.6%) had demonstrated suicide-related behavior (SRB)—either ideation, attempt (suicide and self-inflicted injury), or both. But while vet-
Generic Insulin? Not Yet

Generic insulin has never been available in the U.S. because drug companies have made incremental improvements that kept the product under patent from 1923 to 2014. As a result, says Johns Hopkins researchers, many people who need insulin to control diabetes can’t afford it.

In a *New England Journal of Medicine* study, authors Jeremy Greene, MD, PhD, and Kevin Riggs, MD, MPH, describe insulin as an example of “evergreening,” in which pharmaceutical companies make a series of improvements to important medications to extend their patents for decades. This keeps older versions off the generic market, the authors say, because generic manufacturers have less incentive to make a version of insulin that doctors perceive as obsolete. Newer versions are somewhat better for patients who can afford them, say the authors, but those who can’t suffer painful, costly complications.

“We see generic drugs as a rare success story, providing better quality at a cheaper price,” says Dr. Greene. “And we see the progression from patented drug to generic drug as almost automatic. But the history of insulin highlights the limits of generic competition as a framework for protecting the public health.”

Daily insulin injections can cost $120 to $400 per month without prescription drug insurance. “Insulin is an inconvenient medicine even for people who can afford it,” says Dr. Riggs. “When people can’t afford it, they often stop taking it altogether.”

A University of Toronto team discovered insulin in 1921. In 1923, the university, which held the first patent, gave drug companies the right to manufacture it and to patent improvements. In the 1930s and 1940s, pharmaceutical companies developed long-acting forms that allowed most patients to take a single daily injection. In the 1970s and 1980s, manufacturers improved the purity of cow- and pig-extracted insulin. Since then, several companies have developed synthetic analogs.

Biotech insulin is now the U.S. standard. Patents on the first synthetic insulin expired in 2014, but these newer forms are harder to copy, so unpatented versions will go through a lengthy FDA approval process and will cost more to make. When these insulins come on the market, they may cost 20% to 40% less than the patented versions, Drs. Riggs and Greene write.

Source: Johns Hopkins Medicine, March 18, 2015

Cancer Drug Prices Soar

The prices of leading cancer drugs have risen at rates far outstripping inflation over the last two decades, according to a study published in the *Journal of Economic Perspectives*.

Since 1995, a group of 58 leading cancer drugs has increased in price by 10% annually, even when adjusted for inflation and incremental health benefits, the study finds. In 1995, drugs in this group cost approximately $54,100 for each year of life that they were estimated to add; by 2013, such drugs cost about $207,000 for each additional year of life.

The researchers say rising prices
may reflect a greater social tolerance for significant health care costs. They cite recent cases of political backlash in response to proposals that would limit the ability of public insurance programs to buy expensive, life-extending cancer drugs. On the other hand, patient cost-sharing in medical plans has increased since 1995, limiting the extent to which demand can explain the changes.

The study found a positive correlation between drugs' effectiveness and their prices. Cancer drug prices increased approximately 120% for each additional year of life gained by a patient. Still, price increased more than quality.

In 2013, 100 prominent oncologists suggested that drug companies simply price new drugs within 10% to 20% (usually higher) of the most recent similar drug to reach the market. The paper notes that such assertions are consistent with "reference price models of demand," in which consumers’ decisions to pay involve existing prices rather than a measurement of intrinsic value. It is hard to assess how much money pharmaceutical companies have spent developing specific drugs, the researchers add. Additional factors may also enter the pricing equation.

Overall, the authors conclude: “We believe the direction of causation runs from prices to research and development costs—as prices increase, manufacturers are willing to spend more to discover new drugs—rather than the other way around.”

Source: Massachusetts Institute of Technology, March 18, 2015

... And Oncologists Offer Ideas

Americans with cancer sometimes pay twice as much for the same patented medication as patients in other nations, say the authors of an online article in the Mayo Clinic Proceedings, who suggest a variety of solutions. S. Vincent Rajkumar, MD, of the Mayo Clinic Cancer Center in Rochester, Minnesota, and Hagop Kantarjian, MD, of the MD Anderson Cancer Center in Houston, Texas, wrote that the average price of cancer drugs for about a year of therapy rose from $5,000 to $10,000 before 2000 to more than $100,000 by 2012. During roughly the same period, average U.S. household income fell about 8%.

The authors rebut the major arguments that the pharmaceutical industry uses to justify the high price of cancer drugs, namely, the expense of conducting research and development, the comparative benefits to patients, the assertion that market forces will settle prices to reasonable levels, and the claim that price controls on cancer drugs will stifle innovation.

“The fact that there are five approved drugs to treat an incurable cancer does not mean there is competition,” Dr. Rajkumar says. “Typically, the standard of care is that each drug is used sequentially or in combination, so that each new drug represents a monopoly, with exclusivity granted by patent protection for many years.”

Other reasons for high costs include legislation that prevents Medicare from negotiating drug prices and a lack of value-based pricing, which would tie a drug’s cost to its relative effectiveness compared with other drugs.

The authors recommend potential solutions, some of which are already used in other countries. They suggest allowing Medicare to negotiate drug prices, letting the Patient-Centered Outcomes Research Institute and cancer advocacy groups consider cost in their recommendations, and developing cancer treatment pathways or guidelines that incorporate drugs’ costs and benefits. The FDA or physician panels could recommend target prices based on a drug’s magnitude of benefit, and the importation of drugs from abroad for personal use could be authorized.

The authors suggest eliminating “pay-for-delay” strategies in which a pharmaceutical company with a brand-name drug shares profits on that drug with a generic drug manufacturer for the remainder of a patent period, effectively eliminating a patent challenge and competition. And they envision patient-driven grassroots movements and organizations that would advocate for the interests of cancer patients to balance the advocacy efforts of pharmaceutical companies, insurers, pharmacy outlets, and hospitals.

Sources: Mayo Clinic and Mayo Clinic Proceedings, March 16, 2015

Worms Sniff Out Cancer

Cancers exude odors that dogs can sniff out with high accuracy, but dogs can become distracted in a clinical setting. Nematodes (roundworms) are apparently more focused.

In the Nematode Scent Detection Test (NSDT), Kyushu University researchers tested the cancer-sensing ability of Caenorhabditis elegans on 242 urine samples: 218 controls and 24 samples from patients with cancer. C. elegans performed remarkably well, with 95.8% sensitivity and 95.0% specificity. The positive predictive value was 67.6%; efficiency was 95.0%. The nematode was able to diagnose various cancer types tested at stage 0 or 1.

The researchers tout the NSDT’s “outstanding” characteristics: high accuracy, low cost, painlessness, convenience, and speed. However, despite its nose for cancer, C. elegans can’t identify the organs harboring the cancer cells, the researchers say. Therefore, they suggest the test might best be combined with existing and new methods of diagnosis, such as metabolomic analyses.

Source: PLOS One, March 11, 2015

Unneeded ER Tests Abound

Nearly all of the 435 emergency physicians in a survey admitted ordering too many diagnostic tests out of fear of error, uncertainty, and nonmedical reasons.
The survey, published in *Academic Emergency Medicine*, focused specifically on the use and overuse of imaging tests. More than 85% of respondents said they believed that too many tests are ordered in their own departments, and 97% admitted they ordered “medically unnecessary” radiology tests, which were defined as imaging the physician ordered in response to external pressures and not for optimal medical care.

“I am not surprised by the findings,” said lead author Hemal Kanzaria, MD, a Los Angeles emergency physician. “A lot of what I heard from our survey respondents regarding a fear of being wrong, or missing a low-probability but potentially life-threatening diagnosis, resonates with my own clinical practice.”

Existing protocols and safeguards to prevent overuse clearly aren’t working, the survey results suggest.

“Overall, I interpret our results to suggest that overtesting is not due to physicians’ lack of knowledge or lack of insight or poor medical judgment, but reflects a cultural response both within and outside medicine to uncertainty and error,” Dr. Kanzaria said. “I personally think that to overcome overtesting we need to address our collective intolerance of uncertainty both within medicine and within society at large as well as this culture of blame that triggers the malpractice system.”

Source: HealthLeaders Media, March 30, 2015

**DEVICE NEWS**

**Tiny Blood Pump Approved**

The FDA has approved the Impella 2.5 system (Abiomed, Inc.), a miniature blood pump system intended to help patients maintain stable heart function and circulation during high-risk percutaneous coronary intervention (HRPCI) procedures, such as balloon angioplasty and stenting.

The Impella 2.5 system is meant for temporary use by patients with severe symptomatic coronary artery disease (CAD) and diminished (but stable) heart function who are undergoing HRPCI procedures but are not candidates for surgical coronary bypass treatment. In patients with diminished heart function, the heart pumps less blood than normal every time it beats.

Throughout an HRPCI procedure, the Impella 2.5 system helps maintain stable heart function by drawing blood from the left ventricle and pumping it into the aorta. Before starting a procedure, the interventional cardiologist places the Impella 2.5 using a catheter with the pump loaded into the tip. The tip of the catheter is inserted into one of the body’s large arteries, usually in the leg, and guided through the arteries into the left ventricle. Once the pump is in place, an external controller and monitor turns it on and off, measures heart function, and allows health care providers to adjust the pump to maintain stable heart function and circulation during the procedure.

All patients undergoing HRPCI are at risk for complications related to decreased heart function and lowered blood pressure during the procedure, but patients in need of treatment for extensive or critically located CAD who are already experiencing diminished heart function are at high risk. Unstable heart function during an HRPCI procedure can result in serious complications or prevent completion of the procedure.

The FDA reviewed data for the system in a premarket approval application that included clinical results from the manufacturer’s PROTECT II trial, with supporting information from the multicenter, observational USpella Registry.

The overall data provided evidence that, for patients with severe CAD and diminished heart function, the temporary circulatory support provided by the Impella 2.5 system during an HRPCI procedure may allow a longer and more thorough procedure by preventing episodes of hemodynamic instability due to temporary abnormalities in heart function. Moreover, fewer later adverse events, such as the need for repeat HRPCI procedures, may occur in patients undergoing HRPCI with the pump compared with patients undergoing HRPCI with an intra-aortic balloon pump (IABP).

The Impella 2.5 system can be used as an alternative to the IABP without significantly increasing the safety risks of the HRPCI procedure, the FDA says.

Source: FDA, March 24, 2015

**Ebola Diagnostic Test Authorized**

The FDA has granted emergency use authorization for Xpert Ebola (Cepheid), a molecular diagnostic test for Ebola Zaire virus that delivers results in less than two hours. The test runs in a self-contained cartridge to minimize potential contamination.

In August 2014, the Secretary of Health and Human Services declared that circumstances justified authorization of the emergency use of *in vitro* diagnostics for the detection of Ebola virus infection. The Xpert Ebola test has not been cleared or approved by the FDA, but it will remain available in the U.S. as long as the declared emergency remains in effect or until the test ceases to be authorized by the FDA. The Xpert Ebola test can be used by Clinical Laboratory Improvement Amendments moderate- and high-complexity laboratories in the U.S. or by similarly qualified non-U.S. laboratories.

Source: Cepheid, March 24, 2015

**Evarrest Sealant Use Expanded**

The FDA has approved an additional indication for the Evarrest fibrin sealant patch (Ethicon US, LLC) as an adjunct to hemostasis for the control of bleeding during adult liver surgery.
The Evarrest patch is indicated for use with manual compression as an adjunct to hemostasis to control bleeding during adult liver surgery and soft-tissue bleeding during open retroperitoneal, intra-abdominal, pelvic, and noncardiac thoracic surgery when control of bleeding by standard surgical methods (e.g., suture, ligature, and cautery) are ineffective or impractical.

The flexible composite patch contains embedded human biologics (human thrombin and fibrinogen proteins) that are involved in natural clotting. The biologic components react and initiate a fibrin clot that then integrates into the patch, providing mechanical support and adherence to the wound site.

Surgeons place the Evarrest patch on the bleeding wound surface and apply manual compression for approximately three minutes. The fully bioabsorbable patch remains in the patient's body after surgery.

In clinical studies, the Evarrest patch was more than 94% effective in controlling bleeding across challenging patient types and surgical situations compared with the current standard of care, which was less than 53% effective.

Source: Ethicon US, LLC, April 6, 2015

**IV Therapy Monitoring Device**

The FDA has cleared ivWatch Model 400 (ivWatch LLC), a first-of-its-kind continuous monitoring device that can quickly detect intravenous (IV) infiltration and extravasation.

More than 80% of hospitalized U.S. patients receive peripheral IVs, about 30% of which fail. Many failures are due to infiltrations and extravasations that occur when IV fluids (infusates) inadvertently enter the surrounding tissue. Infiltrations are leaks of less-harmful infusates that can cause pain, redness of the skin, and swelling. Extravasations are leaks of potentially harmful infusates, such as chemotherapy medications. In severe cases, such leaks may result in tissue necrosis, loss of function, amputation, or even death.

The ivWatch uses an optical sensor coupled with a patient monitor. The sensor illuminates tissue near the IV site with visible and near-infrared light; the light returning from the tissue is processed by the monitor using a proprietary algorithm. Caregivers are notified if conditions suggest that an infiltration or extravasation has occurred.

Source: ivWatch, April 9, 2015

**Reprocessing Medical Devices**

The FDA has recommended steps to help manufacturers develop safer reusable medical devices—especially those that pose a greater risk for spreading infections.

Devices intended for repeated use are typically made of durable substances that can withstand reprocessing, a multi-step procedure designed to remove soil and contaminants by cleaning and to inactivate microorganisms by disinfection or sterilization. Complex designs make some reusable devices harder to decontaminate. The FDA issued final industry guidance with recommendations that manufacturers should follow pre-market and post-market for the safe and effective use of reprocessed devices.

A manufacturer's reprocessing instructions are critical to prevent the spread of infections. As part of its regulatory review, the FDA determines whether the manufacturer’s reprocessing instructions are appropriate and can be understood and followed by users. The guidance lists six criteria that should be addressed in the instructions for every reusable device to ensure that users understand and obey the reprocessing instructions.

The guidance recommends that manufacturers consider reprocessing challenges early in the design of devices. Manufacturers will be expected to conduct validation testing to ensure that their cleaning, disinfection, or sterilization instructions will consistently reduce microbial contamination. To support high-level disinfection of duodenoscopes, for instance, reprocessing should result in a six-log reduction in the number of microbes at each of several locations on the scope—that is, a reduction of 99.9999%.

The FDA issued a draft guidance discussing the reprocessing of reusable medical devices in 2011, and considered almost 500 comments before issuing a final guidance that clarifies testing protocols and the data the agency should receive for a premarket submission.

Sources: FDA, March 12, 2015, and March 26, 2015, and FDA guidance document, March 2015

**Olympus Duodenoscope Under the Microscope**

The Olympus TJF-Q180V duodenoscope, implicated in an antibiotic-resistant “superbug” outbreak, was marketed without FDA 510(k) clearance, the agency said. As part of its now-pending application for marketing approval, Olympus submitted new reprocessing instructions for the device that—on the second attempt—satisfied tighter FDA requirements.

Antibiotic-resistant infections have occurred in patients who had procedures with duodenoscopes from three manufacturers, the FDA said. At a Los Angeles hospital, such infections contributed to two deaths.

The FDA is allowing Olympus to continue selling the TJF-Q180V while its application is under review because the agency believes removing the device from the market could leave too few duodenoscopes to meet the annual U.S. demand for about 500,000 procedures. “At this time, FDA has no evidence that the lack
of a 510(k) clearance was associated with the infections,” the agency added.

Olympus gave the FDA validation reports on new reprocessing instructions for the TJF-Q180V in October 2014. The agency found that the disinfection reports “did not demonstrate an adequate safety margin,” so Olympus conducted more tests and submitted new high-level disinfection validation data in late February. The FDA concluded that the new reprocessing instructions, when followed, “demonstrate consistent and reliable cleaning and high-level disinfection.” Olympus sent letters to TJF-Q180V users outlining the new instructions; it will distribute revised user manuals and an additional cleaning brush. The FDA advised facilities using the product to retrain staff and implement the instructions as soon as possible.

Seven patients were infected with carbapenem-resistant Enterobacteriaceae allegedly spread by duodenoscopes and 179 others may have been exposed at Ronald Reagan Medical Center in Los Angeles. At least five lawsuits have been filed against Olympus.

Sources: FDA, March 26, 2015, and Los Angeles Times, March 17, 2015

### Streptococcus A Test Approved

The FDA has approved marketing of the Alere i Strep A test (Alere Inc.), a molecular test that detects group-A Streptococcus (GAS) bacteria in throat-swab specimens in eight minutes or less.

The test uses proprietary Molecular in Minutes (MIM) isothermal nucleic acid amplification technology (iNAT). Unlike polymerase chain reaction (PCR) tests, iNAT does not require complex thermocycling or DNA purification and can therefore deliver PCR-caliber results more quickly, according to Alere.

The clinical performance of the Alere i Strep A test was established in a multicenter U.S. study in which 481 throat-swab specimens were evaluated with the test and compared with standard bacterial culture. The test’s overall sensitivity and specificity were 95.9% (141 of 147) and 94.6% (316 of 334), respectively.

All samples generating discordant results between the Alere i Strep A test and bacterial culture were evaluated by a laboratory-developed real-time PCR assay. Of the six samples negative by the Alere i Strep A test and positive by bacterial culture, four were also negative for GAS by the real-time PCR assay. Of the 18 samples positive by the Alere i Strep A test and negative by bacterial culture, 13 were also positive for GAS by the real-time PCR assay.

Source: Alere Inc., April 2, 2015

### Power Morcellator Use Falls

Eighty-four percent of gynecological surgeons who were using power morcellators in hysterectomies/myomectomies have modified their methods since the FDA warned that the devices could spread undetected cancer during removal of uterine fibroids, a survey found.

Researchers from the Yale University School of Medicine surveyed program faculty of the American Association of Gynecologic Laparoscopists Minimally Invasive Gynecology Surgery Fellowship program from December 2014 to February 2015; 46 of the 161 invited participants completed the online survey.

Of the 43 surgeons (93%) who reported using morcellation during hysterectomies/myomectomies in 2013, 36 (84%) said they changed their surgical approach after the FDA warning in November 2014. Of them, 21 (58%) used minilaparatomy; 18 (50%) used specimen retrieval pouches; 15 (42%) used vaginal extraction in a bag; 14 (39%) reduced the use of laparoscopic supracervical hysterectomy; nine (25%) changed the route of hysterectomy to total laparoscopic hysterectomy; and nine (25%) changed to total abdominal hysterectomy.

“The large proportion of respondents who now use larger incisions or open procedures raises concern about potentially higher patient morbidity,” the researchers wrote. “Safety, efficiency, and long-term outcome data for the innovative surgical techniques that have been adopted are needed urgently.”


### DEVICE SPOTLIGHT

**Kunj Gohil, PharmD, RPh**

**Name:** Watchman Left Atrial Appendage Closure (LAAC) Device  
**Manufacturer:** Boston Scientific, Marlborough, Massachusetts  
**Approval Date:** March 13, 2015  
**Purpose:** The Watchman LAAC Device was approved as an implantable alternative to long-term therapy with warfarin or other oral blood thinners for stroke reduction in patients with non-valvular atrial fibrillation.

**Description:** The Watchman is a one-time implant, approximately the size of a quarter, designed to keep blood clots from the left atrial appendage from entering the bloodstream.

**Benefit:** Boston Scientific has created the first device to be used as an alternative to conventional oral anticoagulants for stroke prevention. Stroke risk is decreased by preventing potentially harmful blood clots from entering the bloodstream. Approval of the Watchman device is supported by a clinical program of studies involving more than 2,400 patients and nearly 6,000 patient-years of follow-up.

Source: www.bostonscientific.com

**Name:** BrightMatter Guide System  
**Manufacturer:** Synaptive Medical, Toronto, Canada  
**Approval Date:** April 7, 2015  
**Purpose:** The BrightMatter Guide continued on page 360
continued from page 326

System is designed to help surgeons guide their tools and inform their surgical approach.

**Description:** This neuro-navigation system displays 3D tractographic visuals of the brain in the operating room. These visuals give surgeons a visual representation of the brain’s internal networks. Uniquely, the system continuously tracks multiple tools throughout a procedure, providing real-time location updates within the surgical cavity.

**Benefit:** The BrightMatter Guide can be considered GPS for the brain. It provides a visual representation of specific complex structures within the brain during complex procedures. With real-time visualization, surgeons will not experience any interruption to their surgical workflow as they try to determine their location.

**Sources:** www.fiercemedicaldevices.com, www.synaptive-medical.com

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**Name:** CoreValve Transaortic Valve Replacement (TVAR) Device

**Manufacturer:** Medtronic, Santa Rosa, California

**Approval Date:** March 31, 2015

**Purpose:** The FDA has expanded this device’s indication to include replacement of patients’ failed artificial aortic valves. This expanded indication is limited to patients who are too frail for open-heart surgery.

**Description:** The CoreValve system is a first-of-its-kind “valve in valve” replacement designed with a self-expanding, conforming frame with a sealing skirt. The valve is created from the tissue of a pig and implanted through a small catheter. Once the valve is in place, it will restore aortic function.

**Benefit:** The CoreValve TVAR Device offers a less-invasive option for high-risk patients. Approval is based on an observational study of 143 patients that showed an improvement in the stroke and mortality rate. Such devices provide treatment to a cohort of patients who may not have any other safe options.

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