NEW DRUG APPROVALS

Ontruzant, a Herceptin Biosimilar

The FDA has approved trastuzumab-dttb (Ontruzant, Samsung Bioepis Company, Ltd.) for HER2-overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. Trastuzumab-dttb, a HER2/neu receptor antagonist, is the third FDA-approved biosimilar of Herceptin (Genentech).

Patients should be selected for therapy based on an FDA-approved companion diagnostic.

Trastuzumab-dttb carries a boxed warning about the risks of cardiomyopathy, serious and fatal infusion reactions, embryo-fetal toxicity, and pulmonary toxicity. Ontruzant will be marketed and distributed in the U.S. by Merck.

Sources: Samsung Bioepis, January 21, 2019; Ontruzant prescribing information, January 2019; FDA, January 18, 2019

Vaxelis, a Combination Vaccine

The FDA has approved Vaxelis (Sanofi/Merck), a vaccine indicated for active immunization to prevent diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *Haemophilus influenzae* type b.

Vaxelis (diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, *Haemophilus* b conjugate [meningococcal protein conjugate] and hepatitis b [recombinant] vaccine) was approved as a three-dose series in children 6 weeks through 4 years of age, prior to their fifth birthday. A 0.5-mL intramuscular injection is administered at 2, 4, and 6 months of age. A three-dose series of Vaxelis does not constitute a primary immunization series against pertussis; an additional dose of a pertussis vaccine is needed.

Solicited adverse reactions following any dose were irritability, crying, injection-site pain, somnolence, injection-site erythema, decreased appetite, fever, injection-site swelling, and vomiting.

Vaxelis will not be commercially available in the U.S. prior to 2020. Sanofi and Merck are working to maximize production to allow for a sustainable supply to meet anticipated demand.

Source: Sanofi, December 26, 2018

Ultomiris for Paroxysmal Nocturnal Hemoglobinuria

Ravulizumab injection (Ultomiris, Alexion Pharmaceuticals) has received FDA approval for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).

PNH is a rare and potentially fatal blood disease, most often diagnosed in young adulthood, that leads to hemolysis. Sudden and recurring episodes lead to the destruction of red blood cells and may be activated by infections or physical exertion. Severe anemia, profound fatigue, shortness of breath, continual episodes of dark-colored urine, kidney disease, and recurrent pain can occur during episodes.

Ravulizumab is a long-acting complement inhibitor that prevents hemolysis when administered once every eight weeks. Eculizumab (Soliris, Alexion), the only other current standard of care, involves treatment every two weeks.

Results from two trials of 246 patients and 197 patients, respectively, demonstrated that ravulizumab has similar results to eculizumab; patients were able to avoid transfusion and had a similar incidence of hemolysis.

Common side effects include headache and upper respiratory infection. Health care providers should use caution when administering ravulizumab to patients with any other systemic infection. Ravulizumab carries a boxed warning about the risk of life-threatening meningococcal infections and sepsis. Providers should comply with the most current recommendations for meningococcal vaccination in patients with complement deficiencies.

The FDA granted ravulizumab priority review and orphan drug designations. The drug is only available through a risk evaluation and mitigation strategy.

Source: FDA, December 21, 2018

Elzonris for Blastic Plasmacytoid Dendritic Cell Neoplasm

Tagraxofusp-erzs infusion (Elzonris, Stemline Therapeutics) has become the first treatment approved by the FDA for blastic plasmacytoid dendritic cell neoplasm (BPDCN) in patients aged 2 years and older.

BPDCN is a rare, aggressive disease of the bone marrow and blood that can affect multiple organs, including the lymph nodes and skin. It often presents as leukemia or evolves into acute leukemia. The disease is more common in men than in women, and in patients 60 years of age and older. Prior to this approval, the standard of care has been chemotherapy followed by bone marrow transplantation—an intensive regimen that many patients cannot tolerate.

The efficacy of tagraxofusp-erzs was studied in two cohorts of patients in a single-arm clinical trial. The first cohort enrolled 13 patients with untreated BPDCN; seven patients (54%) achieved complete remission (CR) or CR with a skin abnormality not indicative of active disease (CRc). The second cohort included 15 patients with relapsed or refractory BPDCN; one patient achieved CR and one achieved CRc.

Common side effects in clinical trials were capillary leak syndrome, nausea, fatigue, peripheral edema, pyrexia, chills, and weight increase. The most common laboratory abnormalities were decreases in lymphocytes, albumin, platelets, hemoglobin, and calcium, and increases in glucose and liver enzymes. Women who are pregnant or breastfeeding should not

take this drug. Tagraxofusp-erzs has a boxed warning about the increased risk of capillary leak syndrome, which may be life-threatening or fatal.

The FDA granted this application breakthrough therapy, priority review, and orphan drug designations.

Source: FDA, December 21, 2018

Asparlas for Acute Lymphoblastic Leukemia

The FDA has approved calaspargase pegol-mknl (Asparlas, Servier Pharmaceuticals LLC), an asparagine-specific enzyme, as a component of a multiagent chemotherapeutic regimen for acute lymphoblastic leukemia (ALL) in patients from 1 month to 21 years of age. This product provides for a longer interval between doses compared with other available pegaspargase products.

Approval was based on a study demonstrating achievement and maintenance of nadir serum asparaginase activity above the level of 0.1 units per milliliter when using calaspargase pegol-mknl, 2,500 units/m^2 intravenously, every three weeks. The pharmacokinetics of calaspargase pegol-mknl were studied when administered in combination with multiagent chemotherapy in 124 patients with B-cell lineage ALL.

The most common adverse reactions were elevated transaminase, increased bilirubin, pancreatitis, and abnormal clotting studies. In a randomized trial, the safety profile of calaspargase pegol-mknl administered every three weeks was similar to that of pegaspargase administered every two weeks.

Calaspargase pegol-mknl received an FDA orphan product designation.

Source: FDA, December 20, 2018

Motegrity for Chronic Idiopathic Constipation

The FDA has approved prucalopride (Motegrity, Shire) as a once-daily, oral treatment for adults with chronic idiopathic constipation (CIC). Prucalopride, a selective serotonin-4 (5-HT_4) receptor agonist, offers a new type of treatment for CIC that enhances colonic peristalsis to increase bowel motility.

Across five of six trials, significantly more patients taking prucalopride achieved the primary endpoint (an average of at least three complete spontaneous bowel movements per week over 12 weeks) than those taking placebo (19–38% for prucalopride [2 mg or less] vs. 10–20% for placebo). A rapid response was seen with peristalsis as early as week one. The FDA has requested that Shire (now part of Takeda) conduct five postmarketing studies evaluating the pharmacokinetics, efficacy, and safety of prucalopride in pediatric, pregnant, and lactating CIC patients.

The most common adverse reactions to prucalopride were headache, abdominal pain, nausea, diarrhea, abdominal distension, dizziness, vomiting, flatulence, and fatigue. However, suicidal ideation and attempts were also reported.

Sources: Shire, December 17, 2018

Generic Approvals

Vigabatrin Tablets

The FDA has approved the marketing of vigabatrin tablets USP, 500 mg, by Teva Pharmaceuticals USA, Inc.—the first generic version of Sabril 500 mg (Lundbeck Pharmaceuticals). Vigabatrin is indicated for the treatment of refractory complex partial seizures in patients 10 years of age and older who have responded inadequately to several alternative treatments.

The FDA had highlighted vigabatrin (along with many other drugs) on a list of off-patent, off-exclusivity branded drugs without approved generics, to emphasize that there were no patents or exclusivities that should impede its approval.

Source: FDA, January 16, 2019

Pimecrolimus Cream

Actavis Laboratories has received FDA approval to market pimecrolimus cream, 1%, the first generic of Elidel Cream, 1% (Valeant Pharmaceuticals North America LLC). Pimecrolimus is indicated as second-line therapy for the short-term and noncontinuous chronic treatment of mild-to-moderate atopic dermatitis.

Source: FDA, December 27, 2018

Methylphenidate Hydrochloride Capsules

The FDA has approved Actavis Elizabeth's marketing of methylphenidate hydrochloride extended-release capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg, for the treatment of attention-deficit/hyperactivity disorder. This is the first generic version of Aptensio XR capsules (Rhodes Pharmaceuticals L.P.) in these dosages.

Source: FDA, December 13, 2018

Hydroxyprogesterone Caproate Injection

The FDA has approved Slayback Pharma LLC's sale of hydroxyprogesterone caproate injection USP, 1,250 mg/5 mL (250 mg/mL) multidose vials for reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The drug is the first generic version of this formulation of Makena (AMAG Pharmaceuticals USA).

Source: FDA, December 12, 2018

Toremifene Citrate Tablets

EirGen Pharma Limited has secured FDA approval to market the first generic toremifene citrate tablets, 60 mg (Eir-101), for the treatment of metastatic breast cancer in postmenopausal women with estrogen-receptor positive or unknown tumors. The branded version is 60-mg Fareston (Kyowa Kirin).

Source: FDA, December 4, 2018

NEW INDICATIONS

New Pediatric Dose of Fluzone Quadrivalent

The FDA has approved the use of Sanofi's 0.5-mL dose of Fluzone Quadrivalent (influenza vaccine) for children aged 6 to 35 months old. The 0.5-mL dose, as well as the 0.25-mL dose, will be available for the 2019–2020 flu season for this expanded age range.

Fluzone Quadrivalent influenza vaccine is indicated for active immunization for the prevention of influenza caused by influenza A subtype viruses and type B virus(es) in the vaccine. Approval was based on data from a phase 4 safety and immunogenicity study in approximately 2,000 children. No new safety concerns were seen, and the 0.5-mL dose induced a robust immune response.

Fluzone Quadrivalent should not be given to anyone who has had a severe allergic reaction to any component of the vaccine, including egg or egg products, or after a previous dose of the vaccine. In addition, it should not be given to anyone who has experienced a severe allergic reaction after a previous dose of any influenza vaccine.

The most common side effects in children include pain, redness, and swelling where the shot is administered; muscle aches; fatigue; and headache. In young children, side effects include irritability, abnormal crying, drowsiness, appetite loss, vomiting, and fever.

Source: Sanofi, January 23, 2019

Cabometyx for Previously Treated Liver Cancer

Cabozantinib tablets (Cabometyx, Exelixis, Inc.) have received FDA approval for the treatment of patients with hepatocellular carcinoma (HCC) who have received previous treatment with sorafenib (Nexavar, Bayer).

The approval was based on results from CELESTIAL, a phase 3, pivotal, randomized, double-blind, placebo-controlled trial of cabozantinib for patients with advanced HCC who previously received sorafenib. Cabozantinib, compared with placebo, improved median overall survival (10.2 vs. 8.0 months), median progression-free survival (5.2 vs. 1.9 months), objective response rate (4% vs. 0.4%), and disease control (64% vs. 33%).

The most common grade 3 or 4 adverse events with cabozantinib were palmar-plantar erythrodysesthesia, hypertension, increased aspartate aminotransferase, fatigue, and diarrhea. Treatment-related fatal adverse events occurred in six patients in the cabozantinib group (hepatic failure, esophagobronchial fistula, portal vein thrombosis, upper gastrointestinal hemorrhage, pulmonary embolism, and hepatorenal syndrome) and in one patient in the placebo group (hepatic failure).

Source: Exelixis, Inc., January 14, 2019

Adacel for Repeat Vaccination

The FDA has approved the expanded use of Adacel (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis [Tdap] vaccine adsorbed) to include repeat vaccination to help protect against tetanus, diphtheria, and pertussis.

Adacel is the first Tdap vaccine in the U.S. approved for a repeat dose in people aged 10 through 64 years old, eight years or more after their first vaccination. Adacel is also the first Tdap vaccine available in a syringe made without natural rubber latex, which may help reduce risk in patients with an allergy.

The FDA licensure was based on clinical data from a study of the safety and effectiveness of repeat Adacel vaccination in adults. In the study of more than 1,300 adults (ages 18 through 64 years), participants received either Adacel vaccine or a tetanus-diphtheria (Td) vaccine eight to 12 years after a previous dose of Adacel vaccine. The study found no significant differences in adverse events between the vaccine groups. A total of 87.7% of Tdap vaccine recipients and 88.0% of Td vaccine recipients reported at least one injection-site reaction.

Source: Sanofi, January 14, 2019

Sprycel for Additional Pediatric ALL Patients

The FDA has expanded the indication for dasatinib tablets (Sprycel, Bristol-Myers Squibb Company) to include the treatment of pediatric patients 1 year old and above with newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) in combination with chemotherapy. Dasatinib is the first second-generation tyrosine kinase inhibitor approved for these patients.

The efficacy of dasatinib with chemotherapy was evaluated in a single cohort of the phase 2, multicenter, single-arm CA180-372 study, which included 78 pediatric patients with newly diagnosed B-cell precursor Ph+ ALL. At three years, the study demonstrated an event-free survival (EFS) binary rate of 64.1%. EFS is the time from start of dasatinib to lack of complete response at the end of the third high-risk block; relapse; secondary malignancy; or death from any cause.

Of 81 patients evaluated for safety, fatal adverse reactions occurred in three (4%), and eight (10%) patients experienced adverse reactions that led to treatment discontinuation, including fungal sepsis, hepatotoxicity of graft-versus-host disease, thrombocytopenia, cytomegalovirus infection, pneumonia, nausea, enteritis, and drug hypersensitivity. The most common serious adverse reactions were pyrexia, febrile neutropenia, mucositis, diarrhea, sepsis, hypotension, infections (bacterial, viral, and fungal), hypersensitivity, vomiting, renal insufficiency, abdominal pain, and musculoskeletal pain.

In pediatric patients, dasatinib was previously approved for Ph+ chronic myeloid leukemia (CML) in the chronic phase, and for certain adults with Ph+ CML or ALL.

Source: Bristol-Myers Squibb, January 2, 2019

Ravicti for Newborns With Urea Cycle Disorder

The FDA has expanded the age range for glycerol phenylbutyrate oral liquid (Ravicti, Horizon Pharma PLC) to include infants younger than 2 months old with a urea cycle disorder (UCD).

Glycerol phenylbutyrate oral liquid is now approved as a nitrogen-binding agent for chronic management of UCDs in adults and children of all ages who cannot be managed by dietary protein restriction and/or amino-acid supplementation alone. The drug must be used with dietary protein restriction and, in some cases, dietary supplements. Glycerol phenylbutyrate is not indicated for acute hyperammonemia in patients with UCDs, and its safety and efficacy for n-acetylglutamate synthase deficiency treatment have not been established.

A study assessed safety, efficacy, and pharmacokinetics in 16 patients with UCDs aged 2 months and younger, who were treated with glycerol phenylbutyrate oral liquid for an average of 10.7 months. Ravicti-treated patients maintained stable ammonia levels relative to their pre-study enrollment. Also, mean ammonia levels were lower during treatment with glycerol phenylbutyrate compared with baseline values.

UCDs are rare genetic disorders in which an enzyme deficiency in the urea cycle causes hyperammonemia that can reach the brain, causing irreversible brain damage, coma, or death.

Source: Horizon Pharma PLC, December 27, 2018

Lynparza for Maintenance Therapy in Ovarian Cancer

Olaparib (Lynparza, AstraZeneca/Merck) has secured FDA approval for the maintenance treatment of women with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Patients should be selected based on an FDA-approved companion diagnostic.

Olaparib is the first PARP inhibitor approved in the first-line maintenance setting for *BRCA*-mutated (BRCAm) advanced ovarian cancer. Approval was based on results from SOLO-1, a randomized, double-blind, placebo-controlled, multicenter trial comparing olaparib with placebo in this population. Progression-free survival was 88% versus 51% at one year and 74% versus 35% at two years. Sixty percent of olaparib patients were progression-free at three years compared to 27% of placebo patients. The most common adverse reactions in patients receiving olaparib were nausea; fatigue; abdominal pain; vomiting; anemia; diarrhea; upper respiratory tract infection, influenza, nasopharyngitis, or bronchitis; constipation; dysgeusia; decreased appetite; dizziness; neutropenia; dyspepsia; dyspnea; urinary tract infection; leukopenia; thrombocytopenia; and stomatitis.

The FDA also approved the BRCAnalysis CDx test (Myriad Genetic Laboratories, Inc.) to identify olaparib-eligible patients. The test's efficacy was based on the SOLO-1 trial population, in whom deleterious or suspected deleterious gBRCAm status was confirmed with prospective or retrospective testing.

Sources: FDA and AstraZeneca, December 19, 2018

Keytruda to Treat Merkel Cell Carcinoma

The FDA has approved pembrolizumab (Keytruda, Merck) for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

The approval was based on the Cancer Immunotherapy Trials Network's CITN-09/KEYNOTE-017 trial, a phase 2, nonrandomized, multicenter, open-label study of 50 patients in this population who had not received prior systemic therapy for their advanced disease. Pembrolizumab monotherapy demonstrated an objective response rate of 56% (complete response rate, 24%; partial response rate, 32%). Among responders, median duration of response (DOR) was not reached; DOR reached or exceeded six months in 96% of responders and reached or exceeded 12 months in 54% of responders.

Pembrolizumab is an anti–programmed-death-1 therapy. Immune-mediated adverse reactions, which may be severe or fatal, can occur with pembrolizumab, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, severe skin reactions, solid-organ transplant rejection, and complications of allogeneic hematopoietic stem-cell transplantation. Adverse reactions occurring in patients with MCC were generally similar to those in patients with melanoma or non–small-cell lung cancer.

This indication received accelerated approval based on tumor response rate and durability of response. Continued approval may be contingent upon the verification and description of clinical benefit in confirmatory trials.

Source: Merck, December 19, 2018

Envarsus XR Immediately Following Kidney Transplant

The FDA has approved a new indication for tacrolimus extended-release tablets (Envarsus XR, Veloxis Pharma-

ceuticals): the prevention of organ rejection in kidney-transplant patients just after surgery, in combination with other immunosuppressants.

Tacrolimus extended-release, taken once daily, was approved in 2015 for the prophylaxis of organ rejection in kidney-transplant patients converted from tacrolimus immediate-release formulations.

A randomized, double-blind, double-dummy, phase 3 study in 543 *de novo* kidney transplant patients demonstrated efficacy and safety comparable to twice-daily tacrolimus (Prograf, Astellas Pharma). After 12 months, the treatment failure rate (a composite endpoint of biopsy-proven acute rejection, graft failure, loss to follow-up, or death) for tacrolimus extended-release was 18.3%, compared with 19.6% for tacrolimus.

As an immunosuppressant, tacrolimus extended-release has a boxed warning about an increased risk for serious infections and malignancies that may lead to hospitalization or death.

Source: Veloxis Pharmaceuticals, December 19, 2018

Nplate for Pediatric Immune Thrombocytopenia

Romiplostim (Nplate, Amgen) has received FDA approval for the treatment of pediatric patients aged 1 year and older who have had immune thrombocytopenia (ITP) for at least six months and an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

The approval was based on two placebo-controlled studies (phase 3 and phase 1/2) in pediatric patients. In the phase 3 study, overall platelet response rates increased with romiplostim (71%) compared with placebo (20%), and durable platelet response occurred more frequently with romiplostim (52%) compared with placebo (10%). In both trials, the most common adverse reactions with romiplostim were contusion, upper respiratory tract infection, and oropharyngeal pain.

Romiplostim was approved in 2008 to treat adults with ITP, a rare and serious autoimmune disease characterized by low platelet counts in the blood and impaired platelet production.

Source: Amgen, December 14, 2018

NEW FORMULATIONS

New Strengths of Apadaz

The FDA has approved two additional strengths of Apadaz (KemPharm, Inc.), an immediate-release combination of the prodrug benzhydrocodone and acetaminophen (APAP). The new dosage strengths—4.08 mg benzhydrocodone/325 mg APAP and 8.16 mg benzhydrocodone/325 mg APAP—join the 6.12 mg benzhydrocodone/325 mg APAP strength approved in February 2018.

Apadaz is intended for the short-term (no more than 14 days) management of acute pain that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. It is the first FDA-approved product to contain a prodrug of hydrocodone.

Apadaz's approval was based in part on pharmacokinetic studies with hydrocodone bitartrate/ibuprofen (Vicoprofen, AbbVie), APAP/tramadol hydrochloride (Ultracet, Janssen), and APAP/hydrocodone bitartrate (Norco, Apil), in which Apadaz demonstrated exposure to hydrocodone and APAP that is expected to result in therapeutic effects equivalent to currently approved immediate-release hydrocodone/APAP combination products, when administered orally as intended.

Source: KemPharm, Inc., January 7, 2019

Inbrija for "Off" Periods In Parkinson's Disease

The FDA has approved levodopa inhalation powder (Inbrija, Acorda Therapeutics) for intermittent treatment of "off" episodes in people with Parkinson's disease who are using carbidopa/levodopa. During off episodes, symptoms return when dopamine levels fall between doses of oral carbidopa/levodopa, the standard oral baseline treatment for the disease.

FDA approval was based on a clinical program that included approximately 900 people with Parkinson's on a carbidopa/levodopa regimen who were experiencing off periods.

The phase 3 pivotal efficacy trial, SPANSM-PD, was a 12-week, randomized, placebo-controlled, double-blind study evaluating the effectiveness of levodopa inhalation powder in patients with mild-to-moderate Parkinson's who were experiencing off periods. Patients showed a statistically significant improvement in motor function at the week 12 visit, as measured by a reduction in the Unified Parkinson's Disease Rating Scale Part III score for levodopa inhalation powder 84 mg compared to placebo at 30 minutes post-dose (–9.83 points and –5.91 points, respectively).

The most common adverse reactions were cough, upper respiratory tract infection, nausea, and discolored sputum.

Source: Acorda Therapeutics, December 21, 2018

ProAir Digihaler Inhalation Powder With Digital Tracking App

The FDA has approved albuterol sulfate 117 mcg inhalation powder (ProAir Digihaler, Teva Pharmaceutical Industries Ltd.), the first digital inhaler with built-in sensors that connects to a companion mobile application and provides inhaler-use information to people with asthma and chronic obstructive pulmonary disease. The product is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway

disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

The product contains built-in sensors that detect when the inhaler is used and measure inspiratory flow. This data is then sent to the companion mobile app using Bluetooth wireless technology so patients can review their data over time and, if desired, share it with their health care professionals. Such data can be important because many patients use their rescue medications incorrectly or too often.

Albuterol sulfate 117 mcg inhalation powder includes a breath-activated, multi-dose dry powder inhaler with albuterol, the most widely used asthma rescue medication. The product does not need to be connected to the mobile app for a patient to take the medicine.

The most common side effects include back pain, body aches and pain, upset stomach, sinus headache, urinary tract infection, heart palpitations, chest pain, tachycardia, shakiness, nervousness, headache, dizziness, sore throat, and runny nose.

Source: Teva Pharmaceutical Industries Ltd., December 21, 2018

FDA REVIEW ACTIVITIES

Breakthrough Therapy Status

Crizanlizumab for Sickle Cell Disease

Novartis has received a breakthrough therapy designation for crizanlizumab (SEG101) for the prevention of vaso-occlusive crises (VOCs) in patients of all genotypes with sickle cell disease.

VOCs—unpredictable and extremely painful events that can lead to serious acute and chronic complications—happen when multiple blood cells stick to each other and to blood vessels, causing blockages. Treatments that make blood cells and blood vessels less sticky may help reduce the number of days that patients experience VOCs.

Crizanlizumab is a monoclonal antibody that binds to the P-selectin molecule on the surface of platelets and endothelium in the blood vessels. It has been shown to inhibit interactions between endothelial cells, platelets, red blood cells, sickled red blood cells, and leukocytes, causing a blockade and thereby preventing these cells from being able to bind to P-selectin, a major driver of the vaso-occlusive process.

The designation for crizanlizumab is based on positive results of the phase 2 SUSTAIN trial, which compared crizanlizumab with placebo in patients with sickle cell disease. Crizanlizumab reduced the median annual rate of VOCs leading to health care visits by 45.3% compared to placebo with or without hydroxyurea therapy. Crizanlizumab also significantly increased the percentage of patients who did not experience any VOCs versus placebo (35.8% vs. 16.9%) during treatment.

Source: Novartis, January 8, 2019

Tarzifyx for Perivascular Epithelioid Cell Tumor

Aadi Bioscience has received a breakthrough therapy designation for Tarzifyx (sirolimus albumin-bound nanoparticles for injectable suspension, ABI-009) for advanced malignant perivascular epithelioid cell tumor (PEComa).

PEComas are a rare subset of soft-tissue tumors, with an undefined cell of origin. They include lymphangioleiomyomatosis, angiomyolipoma, clear-cell "sugar" tumors of the lung, and a variety of morphologically and immunophenotypically similar tumors, which may arise in almost any site of the body.

Malignant PEComas can have an aggressive clinical course, including distant metastases and death. They frequently harbor mutations in the *TSC1* and/or *TSC2* genes that result in the activation of the mammalian target of rapamycin (mTOR)-1 pathway.

The designation was based on data from an ongoing phase 2 registration trial. There have been no prior clinical trials in this disease, and standard chemotherapies used in sarcoma treatment have very limited activity. Anecdotal case reports have suggested clinical benefits of mTOR inhibitors. Tarzifyx is an mTOR inhibitor complexed with human albumin that has significantly higher tumor accumulation and improved efficacy over other mTOR inhibitors in preclinical models.

Source: Aadi Bioscience, January 3, 2019

Satralizumab for Neuromyelitis Optica and Neuromyelitis Optica Spectrum Disorders

The FDA has given a breakthrough therapy designation to Chugai Pharmaceutical Company, Ltd. for satralizumab, an anti–interleukin-6 (IL-6) receptor humanized recycling antibody.

Neuromyelitis optica and neuromyelitis optica spectrum disorders (NMO/NMOSD) are rare, lifelong, and debilitating autoimmune diseases of the central nervous system (CNS), characterized by inflammatory lesions in the optic nerves and spinal cord. Patients frequently experience relapsing disease, with repeated attacks leading to accumulating neurological damage and disability. Symptoms include visual impairment and motor disability. Some NMOSD attacks result in death.

NMOSD pathogenesis is thought to involve AQP4-IgG autoantibody entry into the CNS. However, around one-third of patients with NMOSD are AQP4-IgG seronegative. IL-6 is now emerging as an important factor in NMOSD pathogenesis.

The designation is based on phase 3 study data evaluating satralizumab added to baseline therapy.

Source: Chugai Pharmaceutical Company, Ltd., December 19, 2018

Lonafarnib for Progeria and Progeroid Laminopathies

The FDA has granted a breakthrough therapy designation for lonafarnib (Eiger BioPharmaceuticals) for the treatment of Hutchinson-Gilford progeria syndrome (HGPS, or progeria) and progeroid laminopathies.

Progeria is a rare and rapidly fatal genetic condition of accelerated aging in children. It is caused by a point mutation in the *LMNA* gene, encoding the lamin A protein, that yields the farnesylated aberrant protein, progerin. Lamin A protein is part of the structural scaffolding that holds the nucleus together. Researchers believe that progerin may make the nucleus unstable and that cellular instability may lead to premature aging.

Progeroid laminopathies are genetic conditions of accelerated aging caused by mutations in the lamin A and/or ZMPSTE24 genes, yielding farnesylated proteins that are distinct from progerin. These genetic mutations result in disease manifestations with phenotypes that overlap with, but are distinct from, progeria.

Disease manifestations include severe failure to thrive, a scleroderma-like skin condition, global lipodystrophy, alopecia, joint contractures, skeletal dysplasia, and debilitating strokes. Children with progeria die of arteriosclerosis at an average age of 14.5 years.

Lonafarnib is an orally active inhibitor of farnesyltransferase, an enzyme involved in the modification of proteins through prenylation. Progerin is a farnesylated protein that researchers believe cannot be cleaved, resulting in tight association with the nuclear envelope, which is believed to lead to changes in nuclear envelope morphology and subsequent cellular damage. Lonafarnib blocks the farnesylation of progerin.

Source: Eiger BioPharmaceuticals, Inc., December 19, 2018

Lonafarnib for Hepatitis D Virus Infection

The FDA has given Eiger BioPharmaceuticals a breakthrough therapy designation for lonafarnib, a first-in-class prenylation inhibitor, for the treatment of hepatitis D virus (HDV) infection.

HDV is the most severe form of human viral hepatitis and has no approved treatment. HDV, which occurs only as a coinfection in individuals harboring hepatitis B virus (HBV), leads to more severe liver disease than HBV alone and is associated with accelerated liver fibrosis, liver cancer, and liver failure.

Lonafarnib inhibits the prenylation step of HDV replication inside liver cells and blocks the virus life cycle at the assembly stage.

Lonafarnib has been dosed in more than 120 HDV-infected patients and is in phase 3 development. The designation is supported by data from phase 2 clinical studies of lonafarnib-based treatment regimens in HDV-infected patients that reflect an improvement in liver condition and virological response rarely observed in untreated HDV patients.

Source: Eiger BioPharmaceuticals, Inc., December 17, 2018

Fast-Track Designations

ACX-362E for *C. Difficile* Infection

The FDA has granted fast-track status for ACX-362E (Acurx Pharmaceuticals) for *Clostridium difficile* infection.

ACX-362E is an oral antibiotic, the first of a novel class of DNA polymerase IIIC inhibitors under development by Acurx to treat bacterial infections. Acurx anticipates completing the phase 1 trial in the second quarter of 2019 and is planning to advance ACX-362E into a phase 2 trial in the fourth quarter of 2019.

ACX-362E selectively inhibits the enzyme DNA polymerase IIIC, which is required for bacterial replication and pathogenesis. This enzyme is found only in certain gram-positive bacteria, including *C. difficile*, *Enterococcus*, *Staphylococcus*, and *Streptococcus*. Accordingly, chemically related molecules with the same mechanism of action as ACX-362E have the potential to treat a variety of serious systemic gram-positive infectious diseases.

Source: Acurx Pharmaceuticals, January 16, 2019

Vofatamab for Bladder Cancer

The FDA has given a fast-track designation to vofatamab (Rainier Therapeutics, Inc.) for the treatment of patients with advanced or metastatic FGFR3-positive urothelial-cell carcinoma. Vofatamab (B-701) is an antibody specifically targeted against the fibroblast growth factor receptor 3, a known driver of bladder and other cancers.

An ongoing phase 1b trial is evaluating vofatamab alone and in combination with docetaxel versus docetaxel alone to determine safety and efficacy in patients who have relapsed after, or are refractory to, at least one prior line of chemotherapy.

A phase 2 trial is evaluating vofatamab in combination with pembrolizumab, an immune checkpoint inhibitor, to determine safety, tolerability, and efficacy in the treatment of patients with locally advanced or metastatic bladder cancer who have progressed following platinum-based chemotherapy and have not received prior immune checkpoint-inhibitor therapy.

A third trial planned for later in 2019 will evaluate vofatamab monotherapy in nonmuscle invasive bladder cancer.

Source: Rainier Therapeutics, Inc., January 7, 2019

Baricitinib for Systemic Lupus Erythematosus

Eli Lilly and Company and Incyte Corporation have received a fast-track designation for baricitinib, a treatment

for systemic lupus erythematosus (SLE).

Only one new treatment for SLE has been approved in the U.S. in the past 50 years. Baricitinib is approved in more than 50 countries as Olumiant for the treatment of adults with rheumatoid arthritis.

Lilly is studying two doses of baricitinib in phase 3 SLE trials. The company is also investigating baricitinib as a treatment for moderate-to-severe atopic dermatitis, with phase 3 results projected for the first half of 2019.

Source: Eli Lilly and Company, December 13, 2018

Colistimethate Sodium Powder for Non–Cystic Fibrosis Bronchiectasis

The FDA has granted fast-track and qualified infectious diseases product designations to Zambon for colistimethate sodium powder. The drug is indicated for the prevention of pulmonary exacerbations in adults with non–cystic fibrosis bronchiectasis (NCFB) colonized with *Pseudomonas aeruginosa*.

NCFB is a chronic disease in which phlegm builds up in the airways and becomes infected by bacteria. It results in repeated serious pulmonary infections, which in turn can cause further inflammation and damage in the respiratory organs. Colistimethate sodium, a polymixin antibiotic, is bactericidal against susceptible gram-negative bacteria.

Source: Zambon, December 11, 2018

Elamipretide for Dry Age-Related Macular Degeneration

Stealth BioTherapeutics has secured a fast-track designation for elamipretide, which is indicated for dry age-related macular degeneration (AMD) with geographic atrophy.

Although there are FDA-approved treatments for wet AMD, which affects approximately 10% of people suffering from the disease, there are no approved therapies for dry AMD. Dry AMD with geographic atrophy, an advanced form of dry AMD, is characterized by central blind spots that lead to permanent loss of vision.

A phase 2b study is planned for 2019 to evaluate the safety and efficacy of subcutaneous injections of elamipretide in patients with dry AMD with geographic atrophy.

Source: Stealth BioTherapeutics, December 10, 2018

RP-L102 Gene Therapy for Fanconi Anemia

Rocket Pharmaceuticals, Inc. has been granted fast-track and regenerative medicine advanced therapy (RMAT) designations for RP-L102, a lentiviral vector-based gene therapy for the treatment of Fanconi anemia (FA).

FA is a rare pediatric disease characterized by bone-marrow failure, malformations, and cancer predisposition. The primary cause of death among FA patients is bone-marrow failure, typically during the first decade of life.

Allogeneic hematopoietic stem-cell transplantation (HSCT), when available, corrects the hematologic component of FA, but it requires highly toxic myeloablative conditioning. HSCT is frequently complicated by graft-versus-host disease and increases the risk of solid tumors.

Approximately 60% to 70% of FA patients have a gene mutation that encodes for a protein essential for DNA repair. Mutation in the *FANC-A* gene leads to chromosomal breakage and increased sensitivity to oxidative and environmental stress.

RP-L102's lentiviral vector carries the *FANC-A* gene as part of the PGK-FANCA-WPRE expression cassette, which includes a phosphoglycerate kinase promoter and an optimized woodchuck hepatitis virus posttranscriptional regulatory element. The *ex vivo* administration process begins with the removal and isolation of hematopoietic stem cells. Autologous, genetically modified CD34+ enriched hematopoietic cells are infused back into patients to restore function.

The RMAT designation was based on positive results from an ongoing phase 1/2 clinical trial of RP-L102 in Europe.

Source: Rocket Pharmaceuticals, November 27, 2018

Priority Review Status

Contepo for Complicated UTIs

The FDA has accepted a new drug application and granted priority review for fosfomycin for injection (Contepo, Nabriva Therapeutics PLC) for the treatment of complicated urinary tract infections (cUTIs). The target date for completion of the review is June 30, 2019.

If fosfomycin is approved, it would be a first-in-class intravenous (IV) antibiotic with broad-spectrum activity against gram-negative and gram-positive organisms, including extended spectrum beta-lactamase- (ESBL) producing Enterobacteriaceae and other multidrug-resistant organisms. Annually, some three million gram-negative cUTIs require hospital treatment in the U.S.

A pivotal phase 2/3 clinical trial (ZEUS) met its primary endpoint of statistical noninferiority to piperacillin–tazobactam (Zosyn, Pfizer) in patients who had cUTIs, including acute pyelonephritis.

IV fosfomycin has been used for more than 45 years in Europe for a number of infections, including cUTIs. Contepo's new dosing approach optimizes the drug's pharmacokinetics and pharmacodynamics, strengthening the case for using it as a first-line treatment for cUTIs, including acute pyelonephritis.

In addition to its priority review status, fosfomycin was granted qualified infectious disease product and fast-track designations for the treatment of several serious infections, including cUTI.

Source: Nabriva, January 4, 2019

HTX-011 for Postoperative Pain

The FDA has accepted the new drug application for HTX-011 (Heron Therapeutics) and has granted it a priority review designation. HTX-011 is a long-acting, extended-release formulation of the local anesthetic bupivacaine in a fixed-dose combination with the anti-inflammatory drug meloxicam.

HTX-011 is the first dual-action, fixed-combination product designed for both postoperative pain and inflammation in a single administration at the surgical site.

The application comprises data from phase 2 and 3 clinical trials that included more than 1,000 patients undergoing hernia repair, abdominoplasty, bunionectomy, total knee arthroplasty, and breast augmentation.

Clinical studies have shown that HTX-011 significantly reduces both pain intensity and the need for opioids through 72 hours after surgery compared with placebo and bupivacaine solution, the standard of care. The overall safety profile of HTX-011, administered locally into the surgical site without a needle, is similar to that of bupivacaine solution, with no evidence of meloxicam-related toxicities.

The FDA has set a prescription drug user fee act goal date of April 30, 2019.

Source: Heron Therapeutics, December 31, 2018

Orphan Drug Designations

Apraglutide for Short Bowel Syndrome

The FDA has given an orphan drug designation to apraglutide (Therachon AG) for the treatment of short bowel syndrome (SBS).

SBS results from extensive intestinal resection due to chronic inflammatory bowel disease, acute events (such as mesenteric infarction), or congenital abnormalities. SBS is a severe, chronic condition associated with reduced or complete loss of intestinal function, characterized by malabsorption and malnutrition, which can be life-threatening. Patients typically require 10 to 15 hours of parenteral feeding per day. Parenteral support is associated with infections, blood clots, and poor quality of life.

Apraglutide (FE 203799) is a next-generation, synthetic GLP-2 analog that has undergone extensive preclinical characterization and optimization. Phase 1 single-ascending dose/multiple-ascending dose clinical trials in healthy volunteers have been successfully completed. Apraglutide has a superior pharmacokinetic profile with a half-life of 30 hours, enabling once-weekly dosing.

Apraglutide is being investigated in two phase 2 clinical trials in patients with SBS.

Source: Therachon AG, January 16, 2019

BBT-877 for Idiopathic Pulmonary Fibrosis

Bridge Biotherapeutics Inc. has received an orphan drug designation for BBT-877, a drug for idiopathic pulmonary fibrosis (IPF).

BBT-877 deregulates autotaxin, a key enzyme for generating the lipid-signaling molecule lysophosphatidic acid that is involved in inflammation and fibrosis.

A phase 1 study will assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of BBT-877 in healthy volunteers. The study will be performed in two phases: a single ascending dose phase with five cohorts and a multiple ascending dose phase with three cohorts.

Source: Bridge Biotherapeutics, January 16, 2019

SM08502 for Pancreatic Cancer

SM08502 (Samumed) has received orphan drug status for the treatment of pancreatic cancer. The oral small-molecule Wnt pathway inhibitor may reduce the expression of genes that control the differentiation and multiplication of tumor cells.

The drug is being evaluated in an open-label, multicenter, dose-escalation phase 1 study in 42 adults with advanced solid tumors for whom standard therapy is not available. The study will assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered SM08502 once daily for 28 consecutive days for up to six cycles.

Pancreatic cancer is the fourth leading cause of cancer death in men and women. Symptoms usually appear during the cancer's later stages, which contributes to the high mortality rate.

Sources: MPR and Samumed, January 3, 2019

MYO-102 for Alpha-Sarcoglycanopathy

The FDA has granted an orphan drug designation for MYO-102 (Myonexus Therapeutics), a novel gene therapy candidate for alpha-sarcoglycanopathy, also known as limb girdle muscular dystrophy type 2D (LGMD2D).

LGMD2D is a debilitating condition caused by a defect in the gene that produces the alpha-sarcoglycan protein. Symptoms include inflammation and progressive loss of muscle fiber, which is replaced with fat and fibrotic scars. LGMD2D is believed to affect approximately three in one million people. There is no treatment or cure.

Experimental gene therapy aims to deliver alpha-sarcoglycan genes to permanently restore protein expression, which could significantly improve symptoms and functional ability for patients. Early clinical studies of MYO-102 have demonstrated safety and expression of alpha-sarcoglycan protein. Biopsies six months after treatment with MYO-102 show increased alpha-sarcoglycan expression and presence in muscles.

Source: Myonexus Therapeutics, January 2, 2019

Complete Response Letters

Immunomedics' Sacituzumab Govitecan

Immunomedics, Inc. has received a complete response letter from the FDA on its biologics license application seeking accelerated approval of sacituzumab govitecan for the treatment of patients with metastatic triple-negative breast cancer who have received at least two prior therapies for metastatic disease.

The issues raised in the letter "were exclusively focused on chemistry, manufacturing, and control matters and no new clinical or preclinical data need to be generated," said the company, which plans to request a meeting with the FDA as soon as possible.

Source: Immunomedics, Inc., January 17, 2019

Opsumit for Inoperable Chronic Thromboembolic Pulmonary Hypertension

The FDA has sent a complete response letter to Actelion Pharmaceuticals Ltd. regarding its supplemental new drug application for macitentan (Opsumit) for the treatment of adults with inoperable chronic thromboembolic pulmonary hypertension to improve pulmonary vascular resistance and exercise capacity.

The letter indicates that additional data are needed to evaluate the use of macitentan in this proposed indication. The company said it will work closely with the FDA to review the information outlined in the letter and gain a full understanding of next steps.

Source: Actelion Pharmaceuticals Ltd., January 16, 2019

DRUG SAFETY ISSUES

Lupin Recalls Ceftriaxone

After finding grey particulate matter in reconstituted vials, Lupin Pharmaceuticals, Inc. recalled 42 lots of ceftriaxone for injection, USP. The recall includes five lots of 250-mg, 10 lots of 500-mg, 24 lots of 1-g, and three lots of 2-g product.

Incorrect piercing and using a needle greater than 21 gauge while reconstituting the vial can force rubber flecks from the stopper into the solution. No grey flecks were seen prior to reconstitution of the vial contents. Injecting ceftriaxone (with the rubber particles) could result in vein irritation/phlebitis or pulmonary embolic events that could lead to permanent impairment or injury.

Ceftriaxone for injection, USP, is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Lupin is notifying distributors and arranging for the return of all recalled product lots. A list of lot numbers and expiration dates is available at http://tinyurl.com/LupinDrugRecall.

Source: FDA, January 5, 2019

FDA Warns Genetech Over Stem Cell Products

The FDA has warned Genetech, Inc. of San Diego and its president, Edwin N. Pinos, for marketing stem-cell products without agency approval and for significant deviations from current good tissue practice (CGTP) and current good manufacturing practice (CGMP). Some violations may have led to microbial contamination, the FDA says, potentially causing serious blood infections in patients.

The FDA inspected Genetech's facility in June 2018 and found the company was processing cellular products from human umbilical cord blood for administration by intra-articular injection, intravenous injection, or application directly to the affected tissue to treat a variety of orthopedic conditions. These unapproved products were distributed by Liveyon, LLC of Yorba Linda, California, as ReGen5, ReGen10, and ReGen30.

During the inspection, the FDA documented evidence of significant deviations from CGTP and CGMP requirements in the manufacture of the umbilical cord blood-derived products. The FDA and the Centers for Disease Control and Prevention have received numerous reports of safety issues. The agencies are aware of 12 patients who received Genetech products from Liveyon and subsequently became ill due to blood and other infections caused by bacteria, including *Escherichia coli*.

In September 2018, Liveyon suspended shipment of all products pending an FDA inquiry into the source of the adverse reactions. Liveyon voluntarily recalled all Genetech products it may have distributed.

Source: FDA, November 29, 2018

DEVICE APPROVALS

Rosa Knee System

The FDA has granted 510(k) clearance to the Rosa Knee System (Zimmer Biomet Holdings, Inc.) for robotically-assisted total knee replacement surgeries. The Rosa Knee System features 3D pre-operative planning tools and real-time, intraoperative data on soft-tissue and bone anatomy that is designed to improve bone-cut accuracy and range-of-motion gap analysis to potentially improve flexion and the restoration of natural joint movement.

Rosa Knee employs Zimmer Biomet's Rosa Robotics platform.

Source: Zimmer Biomet Holdings, Inc., January 25, 2019

BD Diabetes Pen Needle

The FDA has given BD (Becton, Dickinson and Company) 510(k) clearance for its second-generation Nano pen needle, designed for more reliable subcutaneous injection of diabetes medications.

The contoured needle base of the new pen needle minimizes the risks from users employing too great a force during an injection by concentrating and then

distributing pressure closely around the injection site. This helps to ensure a more reliable 4-mm target-injection depth compared to similar pen needles.

In addition to decreasing the intramuscular injection risk, the pen needle's new design is easier to use, from attachment to disposal, compared to other models.

Source: BD (Becton, Dickinson and Company), January 24, 2019

Aptima Test for Mycoplasma Genitalium

The FDA recently granted clearance for Hologic, Inc.'s Aptima *Mycoplasma Genitalium* Assay, the first FDA-cleared test for the detection of an increasingly common sexually transmitted infection (STI).

The new assay, cleared through the FDA's *de novo* request process, offers a highly sensitive, specific diagnostic method to identify infections and enable effective treatment.

M. genitalium, which is more common than gonorrhea but underrecognized, was listed as an emerging public health threat in 2015. Current estimates indicate that more than 15% of people in certain high-risk populations are affected.

The absence of an FDA-cleared test has caused *M. genitalium* to be misdiagnosed as other STIs, sometimes resulting in treatment with the wrong antibiotics. Left untreated, infection can lead to infertility and a greater risk of human immunodeficiency virus acquisition and transmission.

Source: Hologic, Inc., January 23, 2019

Abbott Device Can Treat Patent Ductus Arteriosus

The FDA has approved the Amplatzer Piccolo Occluder (Abbott), the first medical device that can be implanted in the tiniest babies (weighing as little as 2 pounds) using a minimally invasive procedure to treat patent ductus arteriosus (PDA). The Amplatzer Piccolo, which is smaller than a pea, offers an option for premature infants and newborns who need corrective treatment and who may be nonresponsive to medical management and at high risk to undergo corrective surgery.

PDA is a potentially life-threatening opening between two blood vessels leading from the heart. This channel, which is present in normally developing fetuses, allows oxygen-rich blood from the mother to circulate throughout the fetus' body. For most infants, the pathway, or duct, seals itself shortly after birth. But in some cases, primarily in babies born prematurely, the PDA fails to close spontaneously.

The Amplatzer Piccolo Occluder is a self-expanding wire mesh device that is inserted through a small incision in the leg and guided through vessels to the heart, where it is placed to seal the opening in the heart. It is designed to allow the physician to insert it through the aortic or pulmonary artery, as well as to retrieve and redeploy the device for optimal placement.

The pivotal ADO II AS trial helped support FDA approval of the device.

Source: Abbott, January 14, 2019

Embrace Smartband Detects Pediatric Epileptic Seizures

The FDA has awarded Embrace (Empatica) 510(k) clearance for use in children. Embrace is an epilepsy smartband that detects patterns in motion and physiological signals that may be associated with generalized tonic-clonic seizures, and immediately alerts caregivers. It is the first non-electroencephalogram-based physiology signal seizure monitoring system to be cleared by the FDA for use in a pediatric population.

In January 2018, Embrace received FDA clearance for seizure monitoring in adults. With the new approval, the watch-like device can be used to detect seizures in children who are aged 6 years and older.

Clinical testing was carried out in an epilepsy monitoring unit among 141 patients with epilepsy, 80 of whom were 6 to 21 years of age; 53 of 54 generalized tonic-clonic seizures were detected by Embrace, an accuracy rate of 98%.

Source: Empatica Inc., January 8, 2019

WEB Aneurysm Embolization

The FDA has given premarket approval to the WEB Aneurysm Embolization System (MicroVention, Inc.) for the treatment of intracranial wide-neck bifurcation aneurysms.

When placed inside the aneurysm sac, the WEB device's proprietary microbraid technology bridges the aneurysm neck, disrupts blood flow, and creates a scaffold for long-lasting treatment.

The pivotal WEB Intrasaccular Therapy Trial (WEB-IT) demonstrated 84.6% adequate occlusion after a safe, single-device procedure for wide-neck bifurcation aneurysms. The system has been used safely in more than 6,000 cases and multiple clinical studies throughout the world.

The device is indicated for use at the middle cerebral artery bifurcation, internal carotid artery terminus, anterior communicating artery complex, or basilar artery apex for the endovascular treatment of adults with saccular, wide-neck, bifurcation intracranial aneurysms with a dome diameter from 3 mm to 10 mm, with either a neck size of 4 mm or greater or a dome-to-neck ratio of greater than one and less than two.

The WEB System was developed by Sequent Medical, Inc., which was acquired in 2016 by Terumo, the parent company of MicroVention.

Source: MicroVention, Inc., January 7, 2019

Miris Human Milk Analyzer

The FDA has permitted marketing of the Miris Human Milk Analyzer (Miris AB), a new diagnostic test to aid health care professionals in measuring breast milk nutrients, including the concentration of fat, carbohydrate, protein, total solids, and energy. The test provides a new tool for the nutritional management of newborns and young infants at risk for growth failure from prematurity or other medical conditions.

Some women's breast milk may not contain sufficient protein and nutrients to meet their infant's needs. Knowing the macronutrient content of the milk may help the health care team and parents make informed decisions on how to fortify it.

The Miris Human Milk Analyzer uses an infrared spectroscopy system to analyze samples of human milk. It is a prescription device intended for use by trained health care personnel at clinical laboratories.

A study tested 112 samples in the machine and compared them to the expected true values obtained by independent methods; both systems provided similar results.

Health care professionals should evaluate test results in conjunction with clinical assessments (such as weight and growth) to inform their discussions with parents in creating a nutritional management plan for an infant or newborn.

The FDA reviewed the test through the *de novo* premarket review pathway, and established special controls to provide for the accuracy and reliability of tests intended to measure the nutritional content of human milk to aid in infants' nutritional management.

Source: FDA, December 21, 2018

Argos Cardiac Output Monitor

A hemodynamic monitoring device for measuring a patient's cardiac output in intensive care units or the operating room has received 510(k) clearance from the FDA.

Retia Medical's Argos monitor uses "multibeat analysis" algorithms and signal processing, which employ a blood pressure waveform to produce a model of an adult patient's circulation. The monitor will provide clinicians with accurate data to help them track the delivery of oxygen and maintain optimal fluid status in high-risk surgical and critically ill patients. In addition, the system integrates with current vital-sign monitors and common electronic medical records platforms.

Many monitors fail to accurately track changes in cardiac output when fluid and vasoactive drug therapy are administered. The Argos device and algorithms avoid this; and, by connecting directly to a vital-sign monitor for information, the monitor eliminates the need for disposables with each use.

Source: FierceBiotech, December 17, 2018

DEVICE SAFETY ISSUES

Essure Surveillance Extended

A post-market surveillance study of women who received the Essure permanent birth control device (Bayer) has been extended from three years to five years at the FDA's request. The FDA also requires additional blood testing of patients enrolled in follow-up visits during the study to learn more about levels of certain markers that can indicate increased inflammation.

Bayer stopped selling and distributing Essure in the U.S. as of December 31, 2018. Sales had declined by 70% after a series of FDA regulatory actions, including the mandated post-market study, the addition of a boxed warning and patient decision checklist to the labeling, and restrictions on the sale and distribution of the device.

The FDA believes that women who have been using Essure successfully to prevent pregnancy can and should continue to do so. Women who suspect the device may be related to symptoms they are experiencing, such as persistent pain, are advised to discuss with their doctor what steps might be appropriate to take.

Source: FDA, December 20, 2018

Duodenoscope Contamination

Interim results from FDA-mandated studies by U.S. duodenoscope manufacturers found higher-than-expected contamination rates after health care workers completed "reprocessing"—the thorough cleaning and disinfection that is required between each use of the device.

Three percent of properly collected samples tested positive for "high-concern" organisms—bacteria often associated with disease, such as *Escherichia coli* or *Staphylococcus aureus*. In addition, up to 3% of samples were positive for low-concern organisms, which are unlikely to cause serious infections but indicate reprocessing failure.

Still, the FDA has seen a steady decline in reports about duodenoscope-associated infections since the agency implemented safety measures to improve reprocessing techniques. The number of reports associated with patient infections peaked in 2015 at 250 and declined to fewer than 100 per year in 2017 and 2018.

For years, the FDA has worked with device manufacturers, public health authorities, hospitals, and providers to help protect patients from infections associated with duodenoscopes. As part of these efforts, the FDA ordered all U.S. duodenoscope manufacturers—Olympus, Fujifilm, and Pentax—to conduct post-market surveillance studies to determine whether health care facilities were able to properly clean and disinfect the devices.

The FDA issued updated recommendations regarding steps that health care providers can take to enhance the reprocessing of duodenoscopes. The agency is also working with developers on new product designs, including disposable components to reduce contamination.

Recently, the FDA and the U.S. Department of Justice brought a criminal action against Olympus for failing to adequately file adverse-event reports involving infections in Europe in 2012 and 2013 that were associated with its TJF-Q180V duodenoscope. After pleading guilty to three counts of distributing misbranded devices in interstate commerce, Olympus was fined $80 million, ordered to forfeit $5 million, and required to undertake enhanced compliance measures.

Source: FDA, December 10, 2018 ■