TRENDS-in-MEDICINE

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by Lynne Peterson

Quick Takes

…Highlights from this week's news relating to drugs and devices in development that are not covered in other *Trends-in-Medicine* reports…

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NOTE: Happy Hanukkah, Merry Christmas, and best wishes for a healthy, happy New Year. This will be the last ***Quick Takes*** for 2019; the next issue will be January 5, 2020.

Top news of the week (*read details in other sections of Quick Takes*)

✓ ROCHE now owns Spark Therapeutics.

✓ **The good news:**

- ALNYLAM PHARMACEUTICALS' lumasiran in primary hyperoxaluria Type 1.
- AMYLYX PHARMACEUTICALS' AMX-0035 in ALS.
- AXSOME THERAPEUTICS' AXS-05 (bupropion + dextromethorphan) in MDD.
- BIOHAVEN PHARMACEUTICALS' vazegepant in acute migraine.
- BIOMARIN PHARMACEUTICAL's vosoritide (BMN-111) in pediatric achondroplasia.
- GLAXOSMITHKLINE
  - Belantamab mafodotin in relapsed/refractory multiple myeloma.
  - Benlysta (belimumab) in active lupus nephritis.
- MERCK MSD's Keytruda (pembrolizumab) – An FDA advisory committee voted 9-4 to recommend expanded approval to treat non-muscle invasive bladder cancer.
- POXEL and SUMITOMO DAINIPPON PHARMA's imeglimin in a Japanese trial in Type 2 diabetes.

✓ **The bad news:**

- BEIGENE's Brukinsa (zanubrutinib) failed in Waldenstrom macroglobulinemia.
- BOEHRINGER INGELHEIM's BI-1467335 – Development was halted over drug-drug interactions.
- GILEAD SCIENCES' firsocostat, cilofexor, and selonsertib, alone and together, in advanced NASH.
- NOVARTIS' fevipiprant (QAW-039) in moderate-to-severe asthma.
- STEALTH BIOTHERAPEUTICS and ALEXION PHARMACEUTICALS' elamipretide in primary mitochondrial myopathy.
- VIIV HEALTHCARE's Cabenuva (cabotegravir + rilpivirine) was rejected by the FDA to treat HIV.

SHORT TAKES

- ADURO BIOTECH's ADU-S100 (MIW-815) – **Novartis**, which had partnered on this intratumoral STING pathway activator, decided not to continue because of the efficacy data (not a safety issue) so far, and has begun winding down an ongoing Phase Ib trial in combination with spartalizumab (PDR-001), an anti-PD-1, in advanced, metastatic treatment-refractory solid tumors or lymphomas.

- ALNYLAM PHARMACEUTICALS' lumasiran, an RNAi targeting glycolate oxidase, met the primary endpoint in the Phase III ILLUMINATE-A trial in primary hyperoxaluria Type 1, significantly reducing urinary oxalate excretion over Months 3-6. All secondary endpoints were also met.

- AMGEN's Xgeva (denosumab) – A study, published in ***JAMA Oncology***, found that the uptake of this subcutaneous bone-modifying agent, has been rapid, capturing nearly 40% of the market in multiple myeloma since approval in early 2018, despite being only non-inferior to – and more expensive than – Novartis' Zometa (zoledronate), which is given IV. While Xgeva may have an advantage in patients with renal dysfunction, the increase in post-approval use was greatest in patients *without* renal dysfunction. The authors offered several explanations, including: newness, lack of awareness that approval was based on non-inferiority, mode of administration, or doctors making more money on Xgeva.

- AMYLYX PHARMACEUTICALS' AMX-0035 significantly slowed disease progression vs. placebo in a Phase II trial in amyotrophic lateral sclerosis (ALS).

- ASPEN SURGICAL bought **Beatty Marketing & Sales**, an orthopedic product provider.

- AVERITAS PHARMA's Qutenza (capsaicin patch) – The FDA accepted a supplemental new drug application (sNDA) for review for this treatment for neuropathic pain associated with diabetic peripheral neuropathy. The PDUFA date is July 13, 2020.

- AXSOME THERAPEUTICS' AXS-05 (bupropion + dextromethorphan) met the primary endpoint in the 327-patient Phase III GEMINI trial in major depressive disorder (MDD), significantly improving depressive symptoms (by MADRS) vs. placebo at Week 6. AXS-05 also met all secondary endpoints.

- BEIGENE's Brukinsa (zanubrutinib), a BTK inhibitor, failed to show superiority to Johnson & Johnson and AbbVie's Imbruvica (ibrutinib) in the Phase III ASPEN trial in Waldenstrom macroglobulinemia, though it was numerically better on the primary endpoint – with lymph nodes shrinking to normal plus a 90% drop in blood protein levels in 28% of Brukinsa patients vs. 19% of Imbruvica patients. Brukinsa's safety profile was better, with fewer cases of irregular heartbeat and fewer adverse event-related discontinuations.

- BIOHAVEN PHARMACEUTICALS' vazegepant, an intranasal small molecule CGRP receptor antagonist, met both co-primary endpoints in a Phase II/III trial in acute migraine, showing superiority to placebo on both pain freedom and freedom from most bothersome symptom at 2 hours. There was pain relief as early as 15 minutes, with benefits sustained for 48 hours.

- BIOMARIN PHARMACEUTICAL's vosoritide (BMN-111) met the primary endpoint in a 121-patient Phase III pediatric trial in achondroplasia, a rare disorder that causes dwarfism, with the children's bones growing faster with this C-type natriuretic peptide vs. placebo at Week 52. Details are expected at a future medical conference.

- BOEHRINGER INGELHEIM's BI-1467335 – The company is discontinuing development of this treatment for non-alcoholic steatohepatitis (NASH), which it licensed from Pharmaxis in 2015, over concern about drug-drug interactions.

- BOSTON SCIENTIFIC – A Delaware court ordered Boston Scientific to complete the merger it wanted to cancel with **Channel Medsystems**.

- BRISTOL-MYERS SQUIBB/CELGENE and ACCELERON PHARMA's Reblozyl (luspatercept-aamt) – The FDA decided the FDA's Oncologic Drugs Advisory Committee did not need to review expanded approval of this erythroid maturation agent in myelodysplastic syndromes, so the planned review on December 18, 2019, was cancelled, and the PDUFA date remains April 4, 2020.

- CATALENT is partnering with **Ethicann** on Zydis technology to formulate a CBD and THC combinational treatment for muscular spasticity in multiple sclerosis patients.

- CATALYST BIOSCIENCES' CB-2782-PEG – **Biogen** bought the exclusive worldwide rights to develop and commercialize this investigational treatment for geographic atrophy associated with dry age-related macular degeneration (dry AMD) as well as Catalyst's other anti-C3 proteases to treat dry AMD.

- CHARLES RIVER LABS is buying **HemaCare**, a cell therapy specialist, for $380 million.

- CONVENTUS ORTHOPAEDICS bought **IntraFuse**, which develops intramedullary implants for repair of minimally-invasive fractures.

- DECIPHERA PHARMACEUTICALS' ripretinib – A new drug application (NDA) was submitted to the FDA for this KIT/PDGFRα inhibitor as a treatment for advanced gastrointestinal stromal tumor (GIST) patients who had prior treatment with Novartis' Gleevec (imatinib), Pfizer's Sutent (sunitinib), and Bayer's Stivarga (regorafenib).

- EKO and the MAYO CLINIC's heart failure detection algorithm in a specialized stethoscope was granted breakthrough device status by the FDA.

- Electronic health records (EHRs) – A study, published in the ***Journal of the American Medical Association***, found that EHRs – even ones that have been certified by the government – may have issues that could lead to patient harm – e.g., an incorrect decimal point in a drug dose (25 mg instead of 2.5 mg), wrongly coded vaccines, inaccurate medication codes, lab results that don't import properly. The study found that nearly 4% of all certified EHRs (275 systems) had the potential for patient harm.

- ELEUSIS BENEFIT CORPORATION's lysergic acid diethylamide (LSD) – The results of a 48-patient, 3-week Phase I trial of this psychedelic in healthy older volunteers, testing microdosing of LSD, were published in the journal ***Psychopharmacology***. The study found the approach appears safe enough to start a trial in Alzheimer's disease patients.

- FIRST LIGHT DIAGNOSTICS' MultiPath – The company got an additional $4.3 million in funding from the Biomedical Advanced Research and Development Authority (BARDA) to develop this diagnostic platform for counting labeled bacterial cells or single molecules for anthrax and urinary tract infection pathogen identification.

- FUJIFILM is buying **Hitachi**'s modality scanner business for $1.56 billion.

- GLP-1 agonists – A study based on data from the World Health Organization's VigiBase case report database of Type 2 diabetics age ≥18, published in ***The Lancet Diabetes & Endocrinology***, found that exendin-based GLP-1 agonists (e.g., AstraZeneca's Byetta, exenatide) had a 2-fold increased risk of anaphylactic reactions vs. human-analog GLP-1 RAs (e.g., Novo Nordisk's Victoza, liraglutide).

- GUARDANT HEALTH's Guardant360, a liquid biopsy test, was granted expanded Medicare coverage across most solid tumor types.

- ILLUMINA – The Federal Trade Commission (FTC) is seeking to block Illumina's planned acquisition of Pacific Biosciences (PacBio), saying it is anti-competitive and monopolistic.

- IMMUNOGEN's mirvetuximab soravtansine – The company said the FDA advised that a positive single-arm pivotal trial might be sufficient to support accelerated approval in ovarian cancer, so the company is planning the SORAYA trial in patients with platinum-resistant ovarian cancer with medium-to-high levels of FR alpha who have already been treated with Roche's Avastin (bevacizumab). This is basically what the FDA recommended in May 2019 after the Phase III FORWARD-1 trial failed.

- MERCK MSD's Keytruda (pembrolizumab) – The FDA's Oncologic Drugs Advisory Committee voted 9-4 to recommend granting expanded approval for this anti-PD-1 to treat non-muscle invasive bladder cancer (NMIBC).

- METRION BIOSCIENCES extended its collaboration with **LifeArc** for another year on research on neuroscience ion channel drug discovery.

- MINERVA NEUROSCIENCES' MIN-117, a 5-HT1A inhibitor, missed the primary endpoint in a 6-week Phase IIb trial in moderate-to-severe major depressive disorder, failing to reduce either MDD symptoms or anxiety symptoms. The company is halting development.

- ONCOLOGY PHARMA is buying ≥50% of **Diagnomics**, which provides sequencing-based genomic testing services.

- PARATEK PHARMACEUTICALS' Nuzyra (omadacycline) – The company got a 5-year contract (that could be extended another 5 years) worth up to $285 million from BARDA to develop this treatment for pulmonary anthrax. The government also has an option to acquire up to 10,000 courses of Nuzyra for the Strategic National Stockpile.

- POXEL and SUMITOMO DAINIPPON PHARMA's imeglimin – In top-line results, this oral oxidative phosphorylation blocker met the primary endpoint in the 714-patient, 52-week, open-label Phase III TIMES-2 trial in Japan in Type 2 diabetes, significantly reducing HbA_{1c} from baseline as monotherapy (-0.46%) and as add-on to a variety of other diabetes drugs (e.g., -0.92% on top of a DPP-4 inhibitor and -0.57% on top of an SGLT2 inhibitor).

- PROTEOSTASIS THERAPEUTICS' dirocaftor (PTI-808) + posenacaftor (PTI-801) ± nesolicaftor (PTI-428) – In the global, 28-day, 68 patient Phase II trial in cystic fibrosis, this triple combination led to an 8-point improvement in FEV_1 vs. placebo in patients with 2 copies of the F508del mutation, with sweat chloride reduced 29 mmol/L vs. placebo. In patients with one copy of F508del, there was no significant improvement in FEV_1, though sweat chloride was significantly reduced. *The data were not as good as for another triplet, Vertex Pharmaceuticals' Trikafta.*

- QURATIS' QTP-101, an investigational tuberculosis vaccine, was licensed to **Bio Farma PT**, an Indonesian state-run company.

- Sales reps – A survey by Cardinal Health Specialty Solutions of 170 hospital and community oncologists found that oncologists are more open to seeing sales reps than other specialties, with 48% allowing sales reps full access, and 45% allowing limited access. What do doctors see as the value added by sales reps? 64% said patient access and assistance programs, 42% said providing staff education, and 24% said patient education materials.

- SEATTLE GENETICS' tucatinib was granted breakthrough therapy designation by the FDA as a treatment for HER2+ metastatic breast cancer.

- SOSEI HEPTARES' HTL-0018318 – The company withdrew plans for a Phase II trial of this muscarinic M1 receptor agonist in dementia with Lewy bodies. The trial had been delayed but now is cancelled.

- STEALTH BIOTHERAPEUTICS and ALEXION PHARMACEUTICALS' elamipretide missed the primary endpoint in the Phase III MMPOWER-3 trial in primary mitochondrial myopathy (PMM), failing to significantly improve performance on the 6-minute walk test or the PMMSA Total Fatigue Score.

- VIIV HEALTHCARE's Cabenuva (cabotegravir + rilpivirine) – The FDA rejected this long-acting (monthly) injectable treatment for HIV, issuing a complete response letter that cited issues with chemistry, manufacturing, and controls, not problems with efficacy or safety.

- WAVE LIFE SCIENCES' suvodirsen – Based on an interim analysis of a Phase I open-label extension trial which found no change from baseline in dystrophin expression, the company discontinued development of this investigational treatment for Duchenne muscular dystrophy patients with exon 51 skipping. Two ongoing trials are being halted. The company also halted development of WVE-N531 for Duchenne with exon 53 skipping.

- ZOGENIX's Fintepla (fenfluramine, ZX-008) – The results of the double-blind, 119-patient Phase III Study1 trial of this amphetamine derivative in Dravet syndrome were published in ***The Lancet***, showing that both doses tested significantly reduced convulsive seizure frequency vs. placebo. Fintepla is currently under review by the FDA.

Very early research news

- Baldness – Researchers at the Icahn School of Medicine at Mount Sinai reported in a paper published in the journal ***Science*** that there may be a way to prevent baldness. The researchers identified a type of muscle that cannot be controlled voluntarily but can potentially be controlled by drugs that block sheath contraction, stop follicle regression, and prevent the loss of existing hair before a new hair can grow. The research shows that contraction of muscle cells around hair follicles is important for the progression of the hair cycle, and this contraction can be manipulated and inhibited.

- Oncology – Researchers at Baylor College of Medicine tested all of the proteins in 500 diverse cancers and discovered that all of them fit into 10 subtypes, each of which is driven by a common set of proteins. They believe their discovery could lead to new ideas for drug development in ovarian, breast, colon, renal, and uterine cancers.

NEWS IN BRIEF

ASTRAZENECA

- **Anifrolumab.** The results of the 362-patient, 3-year Phase III TULIP-2 trial, showing that significantly more systemic lupus erythematosus (SLE) patients achieved a response at Week 52 with monthly administration of this IFR-1 antibody vs. placebo, were published in the ***New England Journal of Medicine***. *Remember, a previous Phase III trial missed the primary endpoint but had positive results on the secondary endpoint, which is the primary endpoint in this trial.*

- **and MERCK MSD's Lynparza (olaparib).** The FDA's Oncologic Drugs Advisory Committee voted 7-5 to recommend approval of this PARP inhibitor as a maintenance treatment for BRCA-mutated metastatic pancreatic cancer. (*Remember that the FDA generally considers a split vote like this as a neutral vote.*)

EPIZYME's tazemetostat

- An NDA was submitted to the FDA for accelerated approval of this EZH2 inhibitor as a ≥3-line treatment for relapsed/refractory follicular lymphoma (with or without EZH2 activating mutations).

- The FDA's Oncologic Drugs Advisory Committee voted unanimously (11-0) to recommend approval to treat epithelioid sarcoma.

GILEAD SCIENCES

- and GALAPAGOS' filgotinib. This oral JAK1 inhibitor was submitted to the FDA to treat moderate-to-severe arthritis – and with a priority review voucher.
- Firsocostat (GS-0976, an acetyl-CoA carboxylase inhibitor), cilofexor (a farnesoid X receptor agonist), and selonsertib (an ASK1 inhibitor). Alone and in combination, all of these drugs missed the primary endpoint in the ATLAS trial in advanced NASH, failing to significantly increase the proportion of patients with a ≥1-stage improvement in fibrosis without NASH worsening vs. placebo.

GLAXOSMITHKLINE

- Belantamab mafodotin (GSK-2857916). In the pivotal, open-label DREAMM-2 trial, published in *The Lancet Oncology*, this anti-BCMA met the primary endpoint, showing a clinically meaningful overall response rate (31% with 2.5 mg/kg) in relapsed/refractory multiple myeloma patients refractory to an immunomodulatory drug, a proteasone inhibitor, and an anti-CD38. GSK has submitted a biologics license application (BLA) for this to the FDA.
- Benlysta (belimumab) met the primary endpoint in the 448-patient Phase III BLISS-LN trial in active lupus nephritis (LN), with significantly more patients achieving PERR at 2 years with Benlysta + standard therapy vs. standard therapy alone (43% vs. 32%).

IONIS PHARMACEUTICALS

- AKCEA's AKCEA-APOCIII-L. Novartis decided ***not*** to exercise its option on this triglyceride-lowering drug, a Generation 2^+ ligand-conjugated antisense (LICA) that inhibits the production of apoC-III. However, Akcea is continuing development, starting with familial chylomicronemia syndrome (FCS).
- MAPTRx, an anti-tau antisense treatment for Alzheimer's disease in Phase I development, was licensed to **Biogen**.

JOHNSON & JOHNSON

- Janssen is partnering with **Resonant Therapeutics** on the discovery and validation of antibody therapeutics for cancer.
- Is taking over **Verb Surgical**, its robotics venture with **Verily**.

NOVARTIS

- Entresto (sacubitril + valsartan). A study, published in *JACC: Heart Failure*, suggests this heart failure drug, an angiotensin receptor-neprilysin inhibitor (ARNI), may not be as effective in African American patients.
- Fevipiprant (QAW-039), an oral once-daily DP2 receptor antagonist, missed the primary endpoint in the pivotal Phase III LUSTER-1 and LUSTER-2 trials in moderate-to-severe asthma, with both doses tested failing to significantly reduce moderate-to-severe exacerbations vs. placebo over 52 weeks. Novartis said it is giving up on the drug.
- Tasigna (nilotinib). A single-center, 75-patient Phase II trial, published in *JAMA Neurology*, found that this c-Abl inhibitor for chronic myeloid leukemia (CML) may have utility in Parkinson's disease. However, another trial (the multicenter NILO-PD study) found nilotinib did not work in Parkinson's.
- Zolgensma (onasemnogene abeparvovec-xioi). Novartis is offering 100 doses of this gene therapy for spinal muscular atrophy through a 2020 lottery in countries where the therapy is not yet approved, with 50 doses reserved for babies age <2.

PHARMAMAR's lurbinectedin

- An NDA for this selective inhibitor of the oncogenic transcription programs (upon which many tumors are particularly dependent) was submitted to the FDA for accelerated approval to treat relapsed small cell lung cancer patients who progressed on platinum-based chemotherapy.
- **Jazz Pharmaceuticals** bought the exclusive rights in the U.S.

PRESCIENT MEDICINE/PRESCIENT METABIOMICS

- Is partnering with **OraSure Technologies/CoreBiome** to develop **LifeKit Prevent**, a microbial assay for colon cancer screening.
- Is collaborating with the Department of Clinical Chemistry at Erasmus MC in The Netherlands to see if **LifeKit Predict** can help predict opioid addiction risk by analyzing 16 genes in the brain's reward pathway.

ROCHE

- Finally was able to complete its $4.3 billion purchase of **Spark Therapeutics**, after getting clearance from both the U.S. Federal Trade Commission and the U.K. Competition and Markets Authority.
- Is collaborating with **Rheos Medicines** on discovery and development of immunometabolism therapeutics.

TAKEDA

- Is collaborating with MiTest Health to expand use of MiTest's personalized risk and outcome prediction tool for patients with Crohn's disease.

- Is collaborating with **Turnstone Biologics** on its viral immunotherapy platform, the vaccinia virus platform.

Vaping update

- The latest numbers from the Centers for Disease Control and Prevention (CDC) indicate there have been 2,506 people hospitalized for EVALI (e-cigarette and vaping-associated lung injury), with 54 deaths.
- Articles were published in both the ***New England Journal of Medicine*** and the CDC's ***Morbidity and Mortality Weekly Report*** with details that Anne Schuchat, MD, principal deputy director of the CDC, reviewed with reporters in a teleconference. On the call, she said:
  - The outbreak really began in June 2019, peaked in September 2019, and is declining but not over.
  - The CDC has concluded that the "explosive outbreak" is due to THC products contaminated with vitamin E acetate. All patients are believed to have vaped THC, despite denials.
  - 38 (*yes,* 38) people died – and dozens worsened – an average of 3-4 days after being released from the hospital post-treatment for EVALI, so the CDC issued updated guidance for clinicians on discharge, including a checklist and a recommendation that patients be re-evaluated within 48 hours of discharge.
  - There were "social media factors that likely played a role" in the outbreak, including ***YouTube*** videos "pushing" how to use vitamin E acetate to cut THC oil.
- As part of Operation Vapor Lock, the FDA and the Drug Enforcement Administration (DEA) seized 44 websites that were advertising the sale of illicit vaping cartridges containing THC. However, so far, none of the products from these sites have been linked to any cases of EVALI.

REGULATORY NEWS

Regulatory tidbits

- **Biologics.** The spending bill that Congress sent to President Trump, and which he signed, expands the definition of a biologic drug to include "chemically synthesized polypeptides [e.g., Novo Nordisk's Victoza (liraglutide) and Lilly's Forteo (teriparatide)], giving them 12 years of exclusivity instead of the 5 years that small molecules get.
- **Consumer misunderstandings.** An FDA survey in 2017 of 1,744 Americans, published in ***Pharmacoepidemiology & Drug Safety***, found most really don't understand drug approvals.

  For instance:
  - Only 25% understood that approval of a new drug does not necessarily mean it will help most people who use it.
  - 17.5% thought an FDA-approved drug means it will cure the condition for which it is prescribed.
  - 69.3% thought all over-the-counter drugs were FDA approved.
  - 24.9% thought the FDA approves dietary supplements.
  - 31% thought the FDA approves direct-to-consumer ads.
- **Drug imports.** The Trump administration is moving to allow imports of cheaper drugs from Canada. ***Endpoints News*** had a great headline that perfectly explains the issue: "Oh Canada! There is no Santa Claus to the north giving out cheap drugs to US patients."
- **FDA guidances**
  - **Effectiveness** – The FDA issued new draft guidance that expands the requirement for a demonstration of substantial evidence of effectiveness for new drugs and biologics.
  - **Pediatric oncology** – The FDA issued new draft guidance outlining requirements for pediatric assessments for some molecularly-targeted oncology drugs and biologics, starting August 18, 2020.
- **Infectious diseases.** The FDA, in collaboration with the National Institutes of Health (NIH) launched CURE ID, a platform for clinicians to report novel uses of existing drugs for difficult-to-treat infectious diseases.
- **Insulin**
  - **Bipartisan legislation** (The Insulin Price Reduction Act) was introduced by Rep. Tom Reed (R-NY) and Diana DeGette (D-CO), co-chairs of the Congressional Diabetes Caucus, that aims for an ~75% reduction in the price of insulin products (from ~$300/vial to ~$68/vial).
  - **LILLY's generic Humalog (insulin lispro).** A report by Sen. Elizabeth Warren (D-MA) and Sen. Richard Blumenthal (D-CT) found that Lilly's program to offer this generic insulin for half-price is a failure because pharmacies don't have it in stock. Their 50-state survey of 190 chain and 196 independent pharmacies found that 83% did not have the authorized, less expensive insulin in stock. In 14 states, none of the up to 8 pharmacies surveyed had it in stock, and in 17 states it was only available in one surveyed pharmacy.
- **Medical devices.** The FDA proposed ending its quarterly reporting of medical device decisions (e.g., listing humanitarian device exemptions and approvals/denials of premarket approval filings) in the Federal Register since these are available on the FDA website.

- **Surprise medical billing.** A provision that would have ended this practice was ***not*** in the final spending bill sent to President Trump.

FDA approvals/clearances

- ASTELLAS and SEATTLE GENETICS' Padcev (enfortumab vedotin-ejfv), a Nectin-4 directed antibody-drug conjugate, was approved to treat advanced urothelial cancer.
- AVADEL PHARMACEUTICALS' Nouress (AV-001), a cysteine hydrochloride injection for treating neonates requiring total parental nutrition, was approved.
- BOSTON SCIENTIFIC's EXALT, a single-use, disposable duodenoscope, was cleared for use.
- MERCK MSD's Ervebo, a vaccine for Ebola Zaire, was approved for people age ≥18.
- MEDTRONIC's Stealth Autoguide, a robotic system for cranial procedures, was cleared for use.
- ORTHOGRID SYSTEMS' PhantomMSK Trauma system for use in implant, instrument, and anatomic alignment during orthopedic procedures was approved.
- PERKINELMER's GSP Neonatal Creatine Kinase-MM kit for newborn screening for Duchenne muscular dystrophy was cleared for use through the de novo pathway.
- PFIZER and ASTELLAS' Xtandi (enzalutamide) was granted expanded approval to treat metastatic castration-sensitive prostate cancer.
- ZURICH MEDTECH/IMANALYTICS' MRIxViP1.5T/3.0T and BCLib extraction and evaluation tool, a modeling tool that could give sponsors more assurance that their products meet the Agency's expectations for MRI compatibility, was qualified through the FDA's Medical Device Development Tools program.

FDA recalls/warnings

- CONFORMIS received a warning letter about failures in its vaporized hydrogen peroxide system for low-temperature sterilizations.
- COOK MEDICAL's CrossCath Support Catheters were recalled (Class I) due to a manufacturing error which could cause the marker bands to dislodge or cause buckling.
- Gabapentinoids – **Pfizer's Neurontin (gabapentin) and Lyrica (pregabalin), Arbor Pharmaceuticals' Horizant (gabapentin), and Assertio Therapeutics' Gralise (gabapentin)** – A MedWatch Safety Alert was added to the FDA website, warning about the possibility of serious breathing problems with all of these drugs in patients with respiratory risk factors.
- GE HEALTHCARE
  - ApexPro telemetry system – The company issued a field safety notice in the U.K. because the central monitoring station or bedside monitor might fail to provide visual or audible electrocardiogram alarms for arrhythmias.
  - Giraffe Incubators and OmniBeds were recalled due to the potential for infants to fall.
- GLENMARK PHARMACEUTICALS' ranitidine – All unexpired lots were recalled due to possible NDMA contamination.
- LANNETT's levetiracetam oral solution – Two lots were recalled due to microbial contamination.
- LIVANOVA's VNS SenTiva Generator System was recalled (Class I) due to a reset error that can cause the system to stop delivering vagal nerve stimulation therapy. The FDA said 4 patients have required revision surgery for failed devices, but there haven't been any deaths reported.
- MEDICINA's IV Luer Slip syringes were recalled due to incorrect packaging.
- MEDTRONIC's SynchroMed II implantable drug infusion pumps were recalled due to the potential presence of foreign particles inside the pump motor assembly – which could cause the pump motor to stall.
- SMITHS MEDICAL's Medfusion 4000 Syringe Pumps were recalled (Class I) due to malfunctioning alarms and the potential interruption of therapy.
- SUN PHARMA received a Form 483 with 8 observations about its plant in Halol, India.

European Regulatory News

- **Medical devices.** The European Parliament and the Council of EU agreed on a 4-year extension for upclassified Class I medical devices to transition to the Medical Device Regulation (MDR).
- ALEVA NEUROTHERAPEUTICS' directSTIM Deep Brain Stimulation System was granted a CE Mark.
- BAEBIES' Finder, a near-patient *in vitro* diagnostic device that can test for hyperbilirubinemia by measuring glucose-6-phosphate dehydrogenase from low blood volume or a single drop of whole blood, was granted a CE Mark.
- HOYA/PENTAX MEDICAL's Discovery, an artificial intelligence-assisted polyp detector, was granted a CE Mark for use during colorectal exams.
- IRRAS' IRRAflow catheter was granted a CE Mark.

- ROCHE's Kadcyla (trastuzumab emtansine) was granted expanded approval by the European Commission to treat HER2+ early breast cancer patients with residual invasive disease after neoadjuvant treatment.

U.K.'s National Institute for Health and Care Excellence (NICE) News

- GW PHARMACEUTICALS' Epidyolex (cannabidiol, Epidiolex in the U.S.) – NICE recommended use as adjunctive therapy for two forms of severe epilepsy (Lennox-Gastaut and Dravet syndromes).
- VIFOR PHARMA's Veltassa (patiromer) – NICE reversed itself and recommended use of this treatment for chronic hyperkalemia.

Regulatory news from other countries

- *China.*
  - GILEAD SCIENCES' Vosevi (sofosbuvir + velpatasvir + voxilaprevir) was approved by the National Medical Products Administration (NMPA) to treat chronic hepatitis C virus (HCV) in adults without cirrhosis and in patients with compensated cirrhosis who failed prior treatment with a direct-acting antiviral.
  - INXMED's IN-10018 – The NMPA approved initiation of a Phase I trial in China of this focal adhesion kinase (FAK) inhibitor in locally advanced/metastatic gastric cancer.

2019 FDA Advisory Committees and Other Regulatory Dates of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
October 14	**Flexion Therapeutics' Zilretta** (FX-006), an extended-release corticosteroid for repeat treatment of osteoarthritis knee pain	PDUFA date **Postponed indefinitely**
December 22	**Bausch Health/Ortho Dermatologics' IDP-123** (tazarotene 0.045% lotion) for acne vulgaris	PDUFA date No decision announced as of December 22
December 24	**Correvio Pharma's Brinavess** (vernakalant), an antiarrhythmic for the rapid conversion of recent onset atrial fibrillation	PDUFA date
December 27	**Durect's Posimir** (bupivacaine extended-release) for post-operative pain	PDUFA date (*Expected to be extended since advisory committee meeting is January 16, 2020)*
December 27	**Intra-Cellular Therapies' lumateperone** for schizophrenia	PDUFA date *Extended from September 27*
2020 FDA Advisory Committees and Other Regulatory Dates of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
January tba	**Merck MSD's Keytruda** (pembrolizumab) – expanded approval to treat high-risk non-muscle invasive bladder cancer	PDUFA date
January tba	**Aimmune Therapeutics' Palforzia** (AR-101) to treat peanut allergy	PDUFA date (***estimated to be in mid-January***)
January 14	**Nektar Therapeutics' oxycodegol** (NKTR-181) for chronic low back pain	FDA's Anesthetic and Analgesic Drug Products Advisory Committee, meeting jointly with the Drug Safety and Risk Management Advisory Committee
January 15	**AM: Esteve Pharmaceuticals' tramadol 44 mg + celecoxib 56 mg** for acute pain requiring an opioid analgesic **PM: Intellipharmaceutics' Aximris XR** (abuse-deterrent oxycodone extended-release), resubmission to manage pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which no alternative treatment is adequate	FDA's Anesthetic and Analgesic Drug Products Advisory Committee, meeting jointly with the Drug Safety and Risk Management Advisory Committee
January 16	**Durect's Posimir** (bupivacaine extended-release) for post-surgical pain	FDA's Anesthetic and Analgesic Drug Products Advisory Committee
January 23	**Epizyme's tazemetostat** for metastatic/locally-advanced epithelioid sarcoma	PDUFA date
January 24	**Merck MSD's Dificid** (fidaxomicin) for *Clostridium difficile* infections	PDUFA date
February 14	**Blueprint Medicines' avapritinib** (BLU-285) for GIST	PDUFA date
February 16	**Agile Therapeutics' Twirla** (AG200-15, 120 μg levonorgestrel + 30 μg ethinyl estradiol), a contraceptive patch	PDUFA date *Extended by the FDA from November 16, 2019*
February 18	**Merck MSD's Keytruda** (pembrolizumab) – 6 sBLAs for a 30-minute Q6W infusion to treat melanoma, Hodgkin's lymphoma, primary mediastinal large B-cell lymphoma, gastric cancer, hepatocellular carcinoma, and Merkel cell carcinoma	PDUFA date
February 19	**Adverse event reporting** using ICH standards	FDA public meeting
February 21	**Alder BioPharmaceuticals' eptinezumab** (ALD-403), a CGRP inhibitor for migraine	PDUFA date
February 21	**Esperion Therapeutics' bempedoic acid** monotherapy to treat hypercholesterolemia	PDUFA date
Feb. 25-26	Discussion of the evolving role of **artificial intelligence in radiological imaging**	FDA public workshop
February 26	**Acacia Pharma's Barhemsys** (IV amisulpride) for post-operative nausea and vomiting (PONV)	PDUFA date
February 26	**Esperion Therapeutics' bempedoic acid in combination with ezetimibe** to treat hypercholesterolemia	PDUFA date
February 27	**BeiGene's zanubrutinib**, a BTK inhibitor for mantle cell lymphoma	PDUFA date
March 3	Development of **individualized therapeutics**	FDA workshop
March 8	**Horizon Therapeutics' teprotumumab** to treat active thyroid eye disease	PDUFA date
March 9	**Intarcia Therapeutics' ITCA-650** (exenatide implant) for Type 2 diabetes	PDUFA date
March 10	**Bristol-Myers Squibb's Opdivo** (nivolumab) **+ Yervoy** (ipilimumab) for advanced hepatocellular carcinoma	PDUFA date
March 10	Patient-focused drug development for **stimulant use disorder**	FDA public meeting
March 15	**Astellas and Seattle Genetics' enfortumab vendotin**, an antibody-drug conjugate for treating metastatic/locally-advanced urothelial cancer	PDUFA date
March 17	**Eton Pharmaceuticals' ET-105** (reformulated lamotrigine) as adjunctive therapy for partial seizures in Lennox-Gastaut syndrome patients	PDUFA date

more - 2020 FDA Advisory Committees and Other Regulatory Dates of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
March 25	**Celgene's ozanimod** (RPC-1063) for relapsing multiple sclerosis	PDUFA date
March 25	**Zogenix's Fintepla** (fenfluramine, ZX-008) for Dravet syndrome	PDUFA date
March 26	**Heron Therapeutics' HTX-011** (bupivacaine + meloxicam) for postoperative pain	PDUFA date
March 26 *postponed*	**Intercept Pharmaceuticals' obeticholic acid** to treat liver fibrosis due to non-alcoholic steatohepatitis (NASH)	PDUFA date postponed, no new date
March 26	**IntelGenx Technologies' Rizaport** (RHB-103) for migraine	PDUFA date
March 28	**Rockwell Medical's Triferic** (ferric pyrophosphate) for anemia	PDUFA date
March tba	**AstraZeneca's Imfinzi** (druvalumab) + tremelimumab for small cell lung cancer	PDUFA date (estimated)
April 4	**Bristol-Myers Squibb/Celgene and Acceleron Pharma's Reblozyl** (luspatercept-aamt) – expanded approval to include very low to intermediate risk myelodysplastic syndrome-associated anemia in patients with ring sideroblasts who require red blood cell transfusions	PDUFA date
April 22 *tentative*	**Intercept Pharmaceuticals' obeticholic acid** to treat liver fibrosis due to non-alcoholic steatohepatitis (NASH)	FDA's Gastrointestinal Drugs Advisory Committee
April 25	**Sanofi's MenQuadfi**, a meningococcal vaccine	PDUFA date
April 26	**Neurocrine Biosciences' opicapone** to treat Parkinson's disease	PDUFA date
April 30	**Sanofi's isatuximab** for relapsed/refractory multiple myeloma	PDUFA date
May 12-13	**Regulatory education for industry**	FDA conference
May 14	**Sunovion Pharmaceuticals' dasotraline** for moderate-to-severe binge eating disorders	PDUFA date
May 24	**Roche's risdiplam** (RG-7916) to treat spinal muscular atrophy	PDUFA date
May 30	**Incyte's pemigatinib** for previously treated, locally-advanced/metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements	PDUFA date
July 13	**Averitas Pharma's Qutenza** (capsaicin patch) – expanded approval to treat neuropathic pain from diabetic peripheral neuropathy	PDUFA date
August 5	**DBV Technologies' Viaskin Peanut** for treating children with peanut allergy	FDA target action date
August 27	**Cassiopea's clascoterone cream 1%**, a topical androgen receptor inhibitor for acne	PDUFA date
Sept. 28-30	Global summit on regulatory science: **Emerging Techologies**	FDA summit **https://aralliance.org/gsrs/**