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: Subscribe to ***Trends-in-Medicine*** for coverage of the **American Society of Nephrology's Kidney Week** and the **Society for Immunotherapy of Cancer (SITC)** meeting, both in Washington, DC. *Remember, most items have a link.*

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

✓ The **FDA** restructured its oncology division.

✓ ICER found three new **migraine drugs** less efficacious and more expensive than triptans.

✓ REGENXBIO's RGX-314, a gene therapy for wet AMD, was put on partial clinical hold by the FDA because of issues with its third-party delivery devices.

✓ **The successful Phase III studies:**

- **ALLENA PHARMACEUTICALS'** **reloxaliase** (ALLN-177) in enteric hyperoxaluria.
- **DAIICHI SANKYO and EXELIXIS'** **esaxerenone** in diabetic nephropathy.
- **PENUMBRA's** **Indigo** in pulmonary embolisms.
- **SANOFI's** **Toujeo** (insulin glargine 300) in kids with Type 1 diabetes.
- **SCYNEXIS'** **ibrexafungerp** in vaginal yeast infection.
- **SPINEOLOGY's** **OptiMesh** in lumbar degenerative disc disease.
- **TAKEDA's** **Ninlaro** (ixazomib) in first-line maintenance multiple myeloma.

✓ **The failed Phase II and III studies:**

- **ANAPTYSBIO's** **etokimab**, an anti-IL-33, in a Phase IIb trial in moderate-to-severe atopic dermatitis.
- **HALOZYME THERAPEUTICS'** **PEGPH20** in a pivotal Phase III trial in first-line metastatic pancreatic cancer.
- **OBSEVA's** **nolasiban** in a Phase IIb trial in women undergoing embryo transfer following *in vitro* fertilization.
- **PFIZER and MERCK KGAA's** **Bavencio** (avelumab) in unresectable/metastatic HER2-negative gastric cancer.
- **ROCHE's** **RG-6206** in Duchenne muscular dystrophy.
- **SUPERNUS PHARMACEUTICALS'** **SPN-810** in impulsive aggression (IA) in ADHD kids.
- **UCB and BIOGEN's** **dapirolizumab pegol** in a Phase IIb trial in moderately-to-severely active SLE.

SHORT TAKES

- AKOYA BIOSCIENCES and **Precision for Medicine** are collaborating on development of liquid biopsy and tissue biomarker assays by combining Akoya's Vectra Polaris system with Precision's ApoStream technology.

- ALLENA PHARMACEUTICALS' reloxaliase (ALLN-177), a first-in-class, recombinant, non-absorbed, orally administered Bacillus subtilis oxalate decarboxylase enzyme, taken 3-5 times/day with meals/snacks, met the primary endpoint in the Phase III URIROX-1 trial in intestinal fat malabsorption, significantly improving 24-hour urinary oxalate excretion (UOx) during Weeks 1-4 vs. placebo (-22.6% vs. -9.7%). And, there was also positive preliminary data from an open-label, single-arm Phase II trial (Study 206) in chronic kidney disease (CKD) patients with enteric hyperoxaluria (a fat malabsorption disorder).

- ALLOGENE THERAPEUTICS is collaborating with **Notch Therapeutics** to use induced pluripotent stem cells (iPSCs) to develop therapies to treat hematologic cancers.

- AMERICAN WELL bought **Aligned Telehealth**, expanding its behavioral health and telepsychiatry offerings.

- ANAPTYSBIO's etokimab, an anti-IL-33, missed the primary endpoint in a Phase IIb trial in moderate-to-severe atopic dermatitis, failing to ease symptoms (itch and skin inflammation) at Week 16. In fact, etokimab was numerically worse than placebo. The company also put a hold on plans for another Phase II trial in severe asthma.

- ASTRAZENECA's Seroquel (quetiapine) and Seroquel XR (quetiapine extended-release) – The European and Russian rights to these antipsychotics were sold to **Cheplapharm**. During the transition, AstraZeneca will continue to manufacture the drugs.

- AVEO ONCOLOGY's tivozanib – The company said that the FDA found an interim survival analysis of the open-label, 350-patient Phase III TIVO-3 trial in renal cell carcinoma is *not* sufficient to file a new drug application (NDA). The company said it still plans to submit the drug to the FDA, along with a revised analysis plan. However, if the final survival analysis, which is expected in May 2020, fails to have a hazard ratio >1.0, the NDA will be withdrawn.

- BIOGEN got exclusive rights to two drugs for treating retinal conditions from **Samsung Bioepis**, its joint venture with **Samsung BioLogics** – SB-11, a biosimilar of Roche's Lucentis (ranibizumab), and SB-15, a biosimilar of Regeneron Pharmaceuticals and Bayer's Eylea (aflibercept). The deal also extends Biogen's rights to China for three anti-TNF biosimilars – AbbVie's Humira (adalimumab), Amgen's Enbrel (etanercept), and Johnson & Johnson's Remicade (infliximab).

- CASSIOPEA's clascoterone cream 1% – The FDA accepted the company's NDA for this topical androgen receptor inhibitor to treat acne. The PDUFA date is August 27, 2020.

- CHEMBIO DIAGNOSTICS' Sure Check HIV Self-Test, a 15-minute test for detecting antibodies to HIV types 1 and 2, was granted prequalification approval by the World Health Organization (WHO).

- Chikungunya vaccines – The FDA's Vaccines and Related Biological Products Advisory Committee held a hearing on November 8 on development of chikungunya vaccines. It was an overview and policy meeting, not a review of a particular vaccine, though several companies working on vaccines made presentations, including Moderna Therapeutics (VRBPAC), Emergency BioSolutions (CHIKV VLP), Themis Bioscience (MV-CHIK), and Valneva (VLA-1553).

- DAIICHI SANKYO and EXELIXIS' esaxerenone – This mineralocorticoid receptor inhibitor met the primary endpoint in the two-armed, parallel group, 455-patient Japanese Phase III ESAX-DN trial in diabetic nephropathy, significantly improving the rate of remission of microalbuminuria at Week 52 (22.1% vs. 4.0% with placebo). Esaxerenone also significantly reduced the rate of urinary albumin to creatinine ratio (UACR) – -58.3% vs. +8.3%, and had lower rate of progression to overt diabetic nephropathy (1.4% vs. 7.5%).

- EVOTEC is collaborating with **Vifor Pharma** on discovery and development of novel nephrology therapeutics.

- Flu update – Walgreens released its first monthly Walgreens Flu Index report, and it showed increased activity compared to this time last year in Alabama, Florida, Louisiana, Mississippi, Nevada, Oklahoma, and Texas. The top three states for flu activity were: Louisiana, Nevada, and Texas.

- HALOZYME THERAPEUTICS' PEGPH20 missed the primary endpoint in the pivotal Phase III HALO-301 trial in first-line metastatic pancreatic cancer, failing to prolong overall survival when added to chemotherapy [Lilly's Gemzar (gemcitabine) + Celgene's Abraxane (nab-paclitaxel)] vs. chemotherapy alone. The company is discontinuing development.

- HORIZON DISCOVERY GROUP is selling its animal research models business unit to **Envigo RMS**.

- ICU MEDICAL bought **Pursuit Vascular**, which gives it Clearguard HD Antimicrobial Barrier Cap for reducing central line-associated bloodstream infections in patients undergoing hemodialysis.

- MED-BOTICS' Oxalert Enhanced Pulse Oximeter, a wrist device for monitoring blood oxygen levels in post-operative inpatients and home users on opioid therapy in an effort to prevent respiratory arrest and death caused by opioid overdose, was granted breakthrough device status by the FDA.

- OBSEVA's nolasiban missed the primary endpoint in a Phase IIb trial in women undergoing embryo transfer following *in vitro* fertilization, failing to increase the ongoing pregnancy rate at Week 10.

- OTTO BOCK HEALTHCARE – The U.S. Federal Trade Commission (FTC) said the company's acquisition of **Freedom Innovations**, substantially lessened competition for microprocessor-driven prosthetic knees, so Freedom Innovations must be divested.

- OWLSTONE MEDICAL is partnering with **Thermo Fisher Scientific** on advancing the application of non-invasive breath sampling for early detection of disease. The companies will integrate Thermo's Orbitrap chromatography mass spectrometry (GC-MS) technology with Owlstone's breath biopsy platform that measures volatile organic compounds (VOCs) in the breath for the detection of disease.

- PENUMBRA's Indigo – This aspiration mechanical thrombectomy system met the primary endpoint in the EXTRACT-PE trial, presented at the Vascular InterVentional Advances (VIVA) meeting in Las Vegas, significantly reducing right ventricular/left ventricular (RV/LV) ratio by 27.3% at 48 hours in pulmonary embolism patients. Competitor devices (e.g., Boston Scientific's EKOS) have previously shown an ~25% reduction. And it was safe, with a low rate of major adverse events (1.7%) at 48 hours.

- PFIZER and MERCK KGAA's Bavencio (avelumab) – In topline results from the 805-patient, Phase III JAVELIN Gastric 100 trial, first-line maintenance therapy in unresectable/metastatic HER2-negative gastric cancer, this PD-L1 inhibitor failed to show superiority to chemotherapy on overall survival either in all patients or in PD-L1+ patients.

- PROMEGA's MSI CDx – **Merck MSD** is collaborating with Promega to develop this test as an on-label microsatellite instability companion diagnostic for identifying solid tumor patients with MSI-high status for treatment with Keytruda (pembrolizumab), a PD-1 inhibitor.

- QIAGEN signed three separate licensing agreements – with Repertoire Genesis; the University of Bonn, Germany; and Stratifyer Molecular Pathology – broadening its immuno-oncology portfolio in companion diagnostics and help with development of T cell and B cell receptor sequencing assays.

- REGENXBIO's RGX-314 – The FDA put a partial clinical hold on this gene therapy program for wet age-related macular degeneration (AMD), delaying the start of a Phase IIb trial, because of issues with the third-party surgical delivery devices.

- SANOFI's Toujeo (insulin glargine 300) – The 463-patient Phase III EDITION JUNIOR trial in children and adolescents (age 6-17) with Type 1 diabetes met the primary endpoint, showing non-inferiority with identical reductions in HbA_{1c} for Toujeo and Lantus (insulin glargine 100) – -0.4% for both. And the rate of hypoglycemia (≤70 mg/dL) was also comparable – 97% vs. 97.8%.

- SCYNEXIS' ibrexafungerp, an oral non-azole antifungal for treating vulvovaginal candidiasis (vagal yeast infection), showed superiority to placebo in the pivotal Phase III VANISH-303 trial, with significantly more patients achieving a complete or partial global response at Day 180. Key secondary endpoints were also met.

- SENTINEL ONCOLOGY's SOL-686 – The company expanded its collaboration with **PhoreMost** to accelerate development of this allosteric Polo-like kinase 1 (PLK1) inhibitor to treat glioma.

- SHRÉIS SCALENE SCIENCES' Cytotron, a device that impedes the growth of malignant tumors through quantum magnetic resonance therapy that induces programmed cell death, was granted breakthrough device designation by the FDA.

- SPINEOLOGY's OptiMesh – The results of the 24-month, 102-patient SCOUT study of this porous graft containment mesh for lumbar degenerative disc disease, presented at the Society for Minimally Invasive Spine Surgery meeting in Las Vegas, showed that the implant significantly reduced lumbar pain and functional limitations at 6, 12, and 24 months, with ~90% of patients reporting excellent or good satisfaction.

- STRYKER is buying **Wright Medical Group** for $4 billion.

- SUPERNUS PHARMACEUTICALS' SPN-810 missed the primary endpoint in a double-blind, parallel-group Phase III trial (P301) in treating impulsive aggression (IA) in attention-deficit/hyperactivity disorder (ADHD) in patients age 6-11, failing to reduce average weekly IA episodes vs. placebo (-47.9% with 18 mg, -58.6% with 36 mg vs. -48.2%

with placebo). As a result, the company is halting enrollment in another Phase III trial (P302) while it studies the P301 data, and the P503 trial in adolescents was put on hold until there are results from P302.

- Tramadol – Public Citizen submitted a citizen petition to the FDA and the Drug Enforcement Administration (DEA), asking that this painkiller – Johnson & Johnson's Ultram and generics (synthetic codeine analogs) – be rescheduled from Schedule IV to Schedule II because of the potential for abuse.

- UBE INDUSTRIES' UD-014, a preclinical small molecule, was licensed to **Novo Nordisk** as a potential treatment for non-alcoholic steatohepatitis (NASH).

NEWS IN BRIEF

BOSTON SCIENTIFIC

The company announced positive data at VIVA for trials of two devices for peripheral artery disease (PAD), and both showed the highest 24-month primary patency reported to date for treating femoropopliteal disease in the U.S. with a drug-coated balloon (DCB) or a drug-eluting stent (DES):

- **Ranger**, a low-dose paclitaxel DCB. A 12-month interim analysis of the RANGER II SFA trial found primary patency was 89.2% vs. 72.9% for angioplasty in treating the superficial femoral artery (SFA) or proximal popliteal artery (PPA). Patients also had a significantly lower target lesion revascularization (6% vs. 17.9%), and comparable all-cause mortality (2.3% vs. 2.5%).

- **Eluvia**, a paclitaxel-eluting stent. The 24-month results from the IMPERIAL trial showed that Eluvia had a primary patency rate of 83.0% vs. 77.1% for Cook's Zilver PTX, and clinically-driven target lesion revascularization (TLR) was 12.7% vs. 20.1% for Zilver, and all-cause mortality 7.1% vs. 8.3%.

GILEAD SCIENCES

- **Biktarvy (bictegravir + emtricitabine + tenofovir alafenamide).** The results of two double-blind, active-controlled Phase III trials (Study 1489 and Study 1490) with a total of 1,274 patients for this triplet therapy vs. dolutegravir-containing regimens in treating newly diagnosed HIV-1 were presented at the European AIDS Conference (EACS) in Basel, Switzerland. Both studies showed good tolerability and high rates of virologic suppression (HIV-1 RNA <50 copies/mL) through Week 144, 82% for Biktarvy vs. 84% for DTG/ABC/3TC and 84% for DTG + F/TAF.

- **and GALAPAGOS' filgotinib.** Data from the FINCH trials of this selective JAK1 inhibitor in moderately-to-severely active rheumatoid arthritis, presented at the American College of Rheumatology (ACR) meeting in Atlanta, showed durable efficacy and safety in methotrexate-naïve patients who didn't respond to other drugs.

- **Firsocostat (GS-0976).** Data presented at the American Association for the Study of Liver Diseases (AASLD) Liver Meeting in Boston showed that giving patients a fenofibrate mitigates triglyceride elevations seen with this ACC treatment for NASH.

- **Truvada (emtricitabine + tenofovir disoproxil fumarate).** The U.S. Department of Health and Human Services (HHS) is taking Gilead to court, seeking damages for infringement of government patents on this HIV drug, now used mostly for pre-exposure prophylaxis (PrEP). HHS alleges Gilead failed to obtain licenses for four patents that the Centers for Disease Control and Prevention (CDC) obtained on research results related to PrEP and has not paid the government any royalties. Gilead argues that all of those patents are invalid.

JOHNSON & JOHNSON/JANSSEN and ARROWHEAD PHARMACEUTICALS' JNJ-73763989 (formerly ARO-HBV)

Phase II data in hepatitis B virus (HBV), to be presented at AASLD on November 11, will show that:

- **Study AROHBV-1001** – a double combination of this RNAi + a nucleos(t)ide analog (NA) had strong activity against HBsAg, HBV DNA, and HBV RNA, but reductions in HBeAg and HBcrAg were less pronounced. There was no difference in response for HBeAg+ and HBeAg- patients.

- In a 12-patient study, the **triple combination** of JNJ-3989 + an NA + JNJ-56136379 (a capsid assembly modulator) was well tolerated, and all patients had robust reductions in HBsAg, HBV DNA, and HBV RNA, but again reductions in HBeAg and HBcrAg were less pronounced. And, again, there was no difference by HBeAg status.

Migraine drugs – the ICER view

The Institute for Clinical and Economic Review (ICER) issued a draft report on three new or soon-to-be-approved migraine drugs – **Biohaven Pharmaceuticals' rimegepant** (an oral CGRP antagonist), **Allergan's ubrogepant** (another CGRP antagonist), and **Lilly's Reyvow** (lasmiditan), a 5-HT 1F agonist – concluding they are similar to each other on efficacy but less effective and more expensive than triptans. Among the ICER findings:

- With all three drugs, more patients achieved freedom from pain by 2 hours vs. placebo. There was no significant difference between the 3 new drugs.

- At 2 hours 55% of patients would be pain-free with lasmiditan, 50% with rimegepant, and 49% with ubrogepant. While that looks good, ICER pointed out that it is even higher with a triptan – 63% with sumatriptan and 72% with eletriptan.
- Likewise, at 24 hours, more patients would be pain free with a triptan.
- None of the 3 new drugs were significantly different from each other on relief from most bothersome symptom. ICER estimated that the proportion of patients with freedom from most bothersome symptom at 2 hours was 40% for lasmiditan, 38% for rimegepant, and 39% for ubrogepant, though all were better than placebo.
- None of the drugs differed from placebo on freedom from nausea at 2 hours.
- ICER was not convinced that the number of migraine days was reduced with these drugs.
- For patients unable to take or non-responsive to a triptan, ICER concluded the three new drugs may be incrementally better than placebo, with a high certainty of at least a small net health benefit.
- For patients who are eligible to use a triptan, the new drugs "are comparable or inferior."
- The incremental cost-effectiveness of the new drugs, relative to each other, "is almost entirely dependent on the cost difference between the three therapies." The triptans are less expensive and more cost-effective.

RADIUS HEALTH

- **Abaloparatide patch.** The company said that, due to slower than expected enrollment, top-line data from the Phase III wearABLe trial of this patch version of injectable Tymlos for osteoporosis will not be available until 2H21.
- **Elacestrant.** Although the company plans to divest its oncology assets, it will continue enrolling patients in the Phase III EMERALD monotherapy trial of this selective estrogen receptor degrader (SERD) in ER+/HER2- breast cancer but will not start any new trials of elacestrant.

ROCHE

- **Lucentis (ranibizumab).** A secondary analysis of the Protocol S trial, published in ***JAMA Ophthalmology***, found that use of this anti-VEGF was more cost-effective at 5 and 10 years than panretinal photocoagulation in eyes with vision-impairing, center-involved diabetic macular edema.
- **RG-6206.** Development of this anti-myostatin adenoectin protein for Duchenne muscular dystrophy was discontinued for futility (not safety) after a pre-planned interim analysis of the Phase II/III SPITFIRE trial.

TAKEDA

- **TAK-003.** The results of a per-protocol analysis of Part 1 of the ongoing 20,071-subject Phase III TIDES trial of this tetravalent dengue vaccine in Asia and Latin America were published in the ***New England Journal of Medicine***, showing efficacy of 80.2% overall and 95.4% efficacy against dengue leading to hospitalization. Among the 28% of patients seronegative at baseline, efficacy was 74.9%. Adverse events were 3.1% for the vaccine vs. 3.8% for placebo.
- Is collaborating with MD Anderson Cancer Center on development of off-the-shelf cord blood-derived CAR-NK therapies with IL-15.
- Is selling a portfolio of non-core over-the-counter and prescription drugs for a number of Near East, Middle East, and African countries to **Acino**.
- Is selling a portion of over-the-counter and prescription drugs for Russia, Georgia, and some other countries in the Commonwealth of Independent States to **Stada**. These include vitamins, food supplements, and some cardiovascular, diabetes, general medicine, and respiratory drugs.
- **Ninlaro (ixazomib)**, an oral protease inhibitor, met the primary endpoint in the 706-patient Phase III TOURMALINE-MM4 trial in first-line maintenance treatment in multiple myeloma patients who did not receive a stem cell transplant but responded to 6-12 months of treatment. *There are no other details, but just maybe they will be at the American Society of Hematology (ASH) meeting in Orlando in December 2019.*
- **Takhzyro (lanadelumab–flyo).** New data from an extension of the 125-patient Phase III HELP trial of this injectable treatment for hereditary angioedema (HAE), acquired from Shire, were presented at the American College of Allergy, Asthma, and Immunology (ACAAI) meeting in Houston TX, are being published in the ***Annals of Allergy, Asthma & Immunology***, showing it continued to prevent HAE attacks "at a rate similar to that in the pivotal portion of the trial." In an exploratory analysis, the maximum attack-free period lasted ≥12 months in 58% of patients and ≥6 months in 78% of patients.

UCB and BIOGEN

Data presented at ACR included:

- ✓ **Dapirolizumab pegol.** The results of a Phase IIb trial in moderately-to-severely active systemic lupus erythematosus (SLE) showed consistent and potentially meaningful improvements on most endpoints vs. placebo. The primary endpoint was ***not*** met, but the companies are planning to go ahead with a Phase III trial of standard-of-care ± dapirolizumab pegol in active SLE.
- ✓ **Bimekizumab.** The 48-week results of a Phase IIb trial in psoriatic arthritis and another trial in ankylosing spondylitis (AS) showed that this IL-17A/17F inhibitor is active in both diseases, with patients achieving low and/or minimal disease activity that was maintained out to Week 48.

UNUM THERAPEUTICS

The company said it will "de-prioritize" its hematologic cancer programs to focus on solid tumors. For hematology this means:

- **ACTR-707.** "Limited" dose escalation will continue for this non-Hodgkin's lymphoma study to inform further development in 2020. Look for additional data from the ATTCK-20-03 trial in combination with Roche's Rituxan (rituximab) at ASH.
- **ACTR-087.** Further dose escalation of this antibody T cell receptor with Seattle Genetics' BCMA-targeting antibody in the Phase I ATTCK-17-01 trial in multiple myeloma will be suspended pending further review.

REGULATORY NEWS

Regulatory tidbits

- **Active pharmaceutical ingredients (APIs).** The director of the FDA's Office of Compliance, Donald Ashley, said the Agency has significant concerns about supply chain data obfuscation, data integrity, and impurity in the API industry, noting that APIs are often distributed without appropriate certificates of analysis, creating problems for supply chain traceability.
- **Ambulatory surgery centers (ASCs).** The Centers for Medicare and Medicaid Services (CMS) issued a final rule that will allow ASCs to get reimbursed, starting January 1, 2020, for fee-for-service Medicare beneficiaries undergoing total knee replacement, mosaicplasty, coronary angioplasty, or cardiac stents.
- **Drug imports.** The Office of Management and Budget is reviewing both the FDA's proposed rule to allow certain drugs to be imported from Canada and some other countries and the draft FDA guidance that would allow manufacturers to import U.S. versions of drugs sold abroad.
- **Drug prices.** Legislation that would crack down on efforts by pharmas to delay competition from generic drugs stalled in the Senate, as did a bill that would require drug companies to put prices in their television ads.
- **Drug safety.** The FDA is asking for public comment on its draft proposal on best practices for postmarket safety surveillance of drugs and biologics.
- **HDEs.** The FDA issued final guidance on its Humanitarian Device Exemption (HDE) program.
- **Medical devices**
  - **Progressive approval.** Sen. Patty Murray (D-WA) and Sen. Elizabeth Warren (D-MA) wrote to the FDA, questioning the Agency's proposed pathway that would allow medical devices to be marketed under progressive approvals. They raised concerns about eligibility criteria, postmarket data quality, and the Agency's ability to remove the devices, if needed, after the provisional approval period has expired.
  - **Technological innovations.** CMS finalized an alternative payment pathway designed to speed Medicare beneficiary access to medical devices considered technological innovations. The agency has approved five devices under the pathway: TriSalus Life Sciences' Surefire Spark Infusion System, Impulse Dynamics' Optimizer System, Procept BioRobotics' AquaBeam System, Wright Medical's Augment Bone Graft, and HumanOptics' ArtificialIris.
- **National security.** Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research, testified before the Health subcommittee of the House Energy and Commerce Committee, telling the panel that the pharmaceutical industry's reliance on Chinese imports is a potential risk to U.S. national security.
- **Orthotic devices.** A report by the HHS' Office of the Inspector General (OIG) found that Medicare and Medicare beneficiaries overpaid for some orthotic devices by $341.7 million dollars from 2012-2015.
- **Physician fee schedule.** CMS released its final Medicare physician fee schedule and quality payment program rule for 2020. Among the changes: Payments to psychologists, social workers, and physical therapists are reduced, while reimbursement is increased for office-based and outpatient evaluation and management visits.
- **Price transparency.** CMS postponed finalizing a rule that would require ***hospitals*** to publish insurer-negotiated rates for healthcare services in order to release the rule along with a proposal for ***health plan*** transparency at a future time.

- Sterilization. The Environmental Protection Agency (EPA) is reviewing national emissions standards for commercial ethylene oxide (EtO) sterilization operations and is seeking public comment before it updates EtO regulations next year.
- Vaping update
  - The CDC is narrowing down on the cause of EVALI (e-cigarette and vaping-associated lung injury), and the "strong culprit" is vitamin E acetate, which was described as "enormously sticky" in the lungs. Vitamin E acetate is an additive, generally to THC, that is not in the commercial vaping products.
  - The number of EVALI cases is now at least 2,051 (in all states but Alaska), with 39 reported deaths across 24 states and the District of Columbia.

FDA reorganization

The FDA has restructured its oncology group. What used to be the Office of Hematology and Oncology Products is now the Office of Oncologic Diseases (OOD), and new divisions have been added. *Don't worry, Richard Pazdur, MD, remains the head of the Oncology Center of Excellence and is the Acting Director of OOD. But "acting" doesn't mean he's going anywhere; he's expected to wear both hats indefinitely.*

Under the **Office of Oncologic Diseases:**

- **Division of Onocology 1** = breast, gynecologic, and genitourinary cancers
- **Diviosn of Oncology 2** = thoracic head & neck, neuro-oncology, rare cancers, pediatric solid tumors
- **Divison of Oncology 3** = GI and superficial cutaneous cancers, melanoma, sarcoma
- **Divison of Hematologic Malignancies 1** = acute leukemia, myelodysplasia, CML
- **Division of Hematologic Malignancies 2** = lymphoma, CLL, multiple myeloma, other plasma cell malignancies
- **Division of Hematologic Oncology Toxicology** = non-clinical review of oncology products

FDA approvals/clearances

- GE HEALTHCARE's Clariscan (gadoterate meglumine), an IV macrocyclic MRI contrast agent, was approved.
- L&K BIOMED/AEGIS SPINE's AccelFix Expandable Cage System, which includes expandable interbody solutions from TLIF/PLIF cages, an expandable lateral interbody, and an expandable interbody, was granted 510(k) clearance for use in spine surgery.
- NOVARTIS' Ziextenzo (pegfilgrastim-bmez) – a biosimilar of Amgen's Neulasta for decreasing infection from febrile neutropenia in patients getting myelosuppresive cancer therapy.
- REDHILL BIOPHARMA's Talicia (RHB-105), a fixed-dose oral combination therapy – two antibiotics (amoxicillin and rifabutin) + a proton pump inhibitor (omeprazole) in one capsule, was approved to treat *H. pylori*.
- SANOFI's Fluzone High-Dose Quadrivalent flu vaccine was granted expanded approval for use in adults age ≥65.
- STRYKER's Sahara, a lateral 3D expandable interbody implant, was granted 510(k) clearance for ≤30 degrees of sagittal spinal correction in skeletally mature patients.
- VELA DIAGNOSTICS' Sentosa SQ HIV Genotyping Assay was cleared for use in detecting resistance mutations using next-generation sequencing (NGS) in HIV-1 patients who are about to start or are already taking antiviral therapy – not for diagnosing HIV.

FDA recalls/warnings

- ABBOTT's CentriMag System for pumping blood through a patient during an open heart procedure was recalled (Class I) due to a calibration system error that may cause the pump to slow/stop, the console screen to go blank, or various inaccurate alarms to go off.
- BAYER's Essure – The FDA issued a reminder to healthcare providers that they are supposed to return any of these contraceptive devices that are unused to the company by the end of 2019.
- BOSTON SCIENTIFIC catheters – Agent paclitaxel-coated balloon catheters, Guidezilla II guide extension catheters, and Emerge and NC Emerge Monorail dilation catheters – were recalled because some batches may not have undergone the hydrophilic coating step during production.
- FAGRON's LETS Gel Kits were voluntarily recalled due to potential microbial contamination.
- MEDTRONIC's MiniMed insulin pump remote controllers (all 1,117 of them) were recalled (Class I) due to potential cybersecurity risks.
- PHILIPS' Forte Gamma Camera System, which is used by healthcare providers to view images of structures/functions inside the body of patients, was recalled because of the potential for the detector to become detached.
- Ranitidine – The latest recalls due to NDMA contamination include:
  - American Health Packaging's ranitidine syrup.
  - Aurobindo Pharma's ranitidine tablets and syrup.

- ZIMMER BIOMET's Rosa Brain, a robot-assisted neurosurgery system, was recalled (Class I) due to a software problem that could cause incorrect robotic arm positioning.
- ZYDUS CADILA received a warning letter about contamination issues at its injectables plant in Moraiya, India.

European Regulatory News

- Biosimilars – The European Medicines Agency (EMA) and the European Commission released a guide in 23 languages about biosimilars for both patients and healthcare professionals.
- MDR – A RAPS/KPMG survey of >200 medical device industry leaders found that only 27% expect to be fully compliant with the new European Medical Devices Regulations (MDR) when they go into effect on May 26, 2020. About half of the respondents said they plan to take advantage of transitional provisions that will allow continued marketing of their current devices through 2024, and nearly half said the MDR is likely to cause them to withdraw or discontinue their devices in that market.
- JOHNSON & JOHNSON's Ebola Zaire vaccine – J&J submitted two marketing authorisation applications (MAAs) to the EMA – one for Ad26.ZEBOV (the first of 2 doses), and another for Bavarian Nordic's MVA-BN-Filo (the second dose).

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

- JOHNSON & JOHNSON's Imbruvica (ibrutinib) – NICE said it was unable to make a recommendation about the use of this BTK inhibitor with Roche's MabThera (rituximab, Rituxan in the U.S.) to treat Waldenstrom's macroglobulinaemia because the company did not provide an evidence submission, but NICE said it would review the drug if and when J&J makes a submission.

Regulatory news from other countries

- *Canada.* JOHNSON & JOHNSON's Darzalex (daratumumab) – Health Canada approved the use of this anti-CD38 in combination with Celgene's Revlimid (lenalidomide) + dexamethasone to treat newly diagnosed multiple myeloma patients ineligible for a stem cell transplant.
- *China.*
  - BIOLIDICS' ClearCell FX1 System, a liquid biopsy platform for analyzing and quantifying cancer cells in blood, was granted Class I registration by the National Medical Products Administration, allowing use for *in vitro* diagnostic testing in hospitals and laboratories.
  - LUCENCE DIAGNOSTICS is collaborating with **MEDx Translational Medicine** on development of companion diagnostic cancer tests using Lucence's PD-L1 rearrangement-identifying technology and multiplex immunofluorescence technology to predict anti-PD-1/PD-L1 therapy outcomes.
- *Pakistan.* The Drug Regulatory Authority of Pakistan (DRAP) issued draft guidance on its priority review and accelerated approval processes, creating two pathways – one for priority review and another for conditional marketing approval.

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 osteoarthritis knee pain	PDUFA date **Postponed indefinitely**
October 21	**Eton Pharmaceuticals' ET-202** (phenylephrine) for low blood pressure	PDUFA date **No decision announced yet**
October 31	**Adamis Pharmaceuticals' Zimhi** (injectable higher dose naloxone) for opioid overdose	PDUFA date **No decision announced yet**
November 12	Advancing development of pediatric therapeutics: **clinical trial endpoints for rare diseases**	FDA workshop by the Office of Pediatric Therapeutics
November 13	**Boehringer Ingelheim's Jardiance** (empagliflozin) – expanded approval for use in Type 1 diabetes	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
Nov. 13-14	Immunological responses to **implanted metal-containing medical devices**	FDA's Immunology Devices Advisory Committee
November 14	**Amarin's Vascepa** (icosapent ethyl) – expanded approval to reduce cardiovascular risk in statin-managed patients with high triglycerides	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
November 14	**Shionogi's Fetroja** (cefiderocol lyophilized powder) for complicated urinary tract infections	PDUFA date
November 16	**Agile Therapeutics' Twirla** (AG200-15, 120 μg levonorgestrel + 30 μfg ethinyl estradiol), a contraceptive	PDUFA date
Nov. 18-19	Discussion of **antibacterial drug development** – status and how to enhance enrollment	FDA-IDSA-NIAID and Pew joint workshop
November 21	Strategies to improve **health equity** amidst the opioid crisis	FDA public meeting
November 22	Discussion of **cold stored platelet products** intended for transfusion	FDA's Blood Products Advisory Committee
November 30	**Aquestive Therapeutics' Exservan** (riluzole oral film) for ALS	PDUFA date
December 4	**Celgene and Acceleron Pharma's luspatercept** for beta-thalassemia-associated anemia	PDUFA date
December 4-5	**Prescription drug labeling**	FDA conference for industry
December 5-6	**Repurposing off-patent drugs** – research and regulatory challenges	FDA workshop
December 6	**Patient-focused drug development**	FDA public workshop
Dec. 12-13	**Global bioequivalence harmonization initiative**	FDA workshop in collaboration with American Association of Pharmaceutical Scientists and European Federation for Pharmaceutical Sciences
December 15	**Avadel Pharmaceuticals' AV-001** (once-nightly sodium oxybate), a hospital product	PDUFA date *Extended by 3 months from September 15*
December 16	**Amgen's ABP-710**, a biosimilar of Johnson & Johnson's Remicade (infliximab) for moderate-to-severe rheumatoid arthritis and more	PDUFA date
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
December 28	**Amarin's Vascepa** (icosapent ethyl) – expanded approval to reduce cardiovascular risk in statin-managed patients with high triglycerides	PDUFA date *Expected extension from September 28, 2019*

2020 FDA Advisory Committees and Other Regulatory Dates of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
January 23	**Epizyme's tazemetostat** for metastatic/locally-advanced epithelioid sarcoma	PDUFA date
February 4	**Alnylam Pharmaceuticals' givosiran** for acute hepatic porphyria	PDUFA date
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	**Esperion Therapeutics' bempedoic acid** monotherapy to treat hypercholesterolemia	PDUFA date
February 26	**Esperion Therapeutics' bempedoic acid in combination with ezetimibe** to treat hypercholesterolemia	PDUFA date
February 26	**Acacia Pharma's Barhemsys** (IV amisulpride) for post-operative nausea and vomiting (PONV)	PDUFA date
February 27	**BeiGene's zanubrutinib**, a BTK inhibitor for mantle cell lymphoma	PDUFA date
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 15	**Astellas and Seattle Genetics' enfortumab vendotin**, an antibody-drug conjugate for treating metastatic/locally-advanced urothelial cancer	PDUFA date
March 25	**Celgene's ozanimod** (RPC-1063) for relapsing multiple sclerosis	PDUFA date
March 26	**Heron Therapeutics' HTX-011** (bupivacaine + meloxicam) for postoperative pain	PDUFA date
April 4	**Celgene and Acceleron Pharma's luspatercept** for myelodysplastic syndrome-associated anemia	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
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