TRENDS-in-MEDICINE

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

✓ NOVARTIS is buying The Medicines Company for $9.7 billion.

✓ **The positive news:**

- ACADIA PHARMACEUTICALS' Nuplazid (pimavanserin) met the primary endpoint in a Phase II trial in schizophrenia patients with primarily negative symptoms.
- TAKEDA's TAK-003, a tetravalent dengue vaccine, met the primary endpoint in a Phase III trial in children.

✓ **The negative news:**

- ADAMIS PHARMACEUTICALS' Zimhi (high-dose naloxone injection) was rejected by the FDA.
- CYMABAY THERAPEUTICS' seladelpar – Due to safety issues in a NASH trial, all development was halted.
- LA JOLLA PHARMACEUTICAL's LJPC-401 (synthetic human hepcidin) – A pivotal trial for iron overload in beta thalassemia was halted for lack of efficacy.

SHORT TAKES

■ ACADIA PHARMACEUTICALS' Nuplazid (pimavanserin) – In top-line results from the 26-week, double-blind, 403-patient Phase II ADVANCE trial in schizophrenia patients with primarily negative symptoms, this atypical antipsychotic met the primary endpoint, significantly improving negative symptoms (NSA-16) vs. placebo (-10.4 vs. -8.5). However, pimavanserin missed the key secondary endpoint, failing to improve the Personal and Social Performance (PSP) scale vs. placebo.

■ ADAMIS PHARMACEUTICALS' Zimhi (high-dose naloxone injection) was rejected by the FDA, which issued a complete response letter (CRL), citing issues with chemistry, manufacturing, and controls (CMC).

■ AMOYDX is collaborating with Eisai on development of companion diagnostics.

■ Amyotrophic lateral sclerosis (ALS) – Cromolyn sodium, a generic drug used to treat the symptoms of asthma and mastocytosis, may have a new use – treating ALS and Alzheimer's disease. Researchers at Massachusetts General Hospital reported in the journal ***Scientific Reports*** that their mouse studies show injected cromolyn inhibits amyloid beta aggregation and inflammation.

■ ARDELYX expanded its partnership with Kyowa Kirin to include a two-year research collaboration on identification and design of compounds against two undisclosed targets.

- ASAHI KASEI is buying Veloxis Pharmaceuticals for $1.3 billion.

- ASLAN PHARMACEUTICALS' ASLAN-003 – Preclinical data, published in the *Haematologica Journal*, for this dihydro-orotate dehydrogenase (DHODH) inhibitor showed *potential* for treating acute myeloid leukemia (AML).

- ASTRAZENECA is collaborating with Novoheart to turn Novoheart's human ventricular cardiac organoid chamber (hvCOC) – "human heart-in-a-jar" – technology into a preclinical model that mimics heart failure with preserved ejection fraction (HFpEF), a condition for which there currently is no effective therapy.

- ASURAGEN is collaborating with Wave Life Sciences on development of a companion diagnostic for Wave's allele-selective therapeutic programs for Huntington's disease using Asuragen's AmplideX PCR technology to create a diagnostic tool that can measure HTT CAG repeat length.

- Cell and gene therapy manufacturing – According to the Alliance for Regenerative Medicine, there were 1,052 cell and gene therapy clinical trials underway in 3Q19, and the large viral vector manufacturers – Lonza, Thermo Fisher Scientific, and Catalent – reportedly already have a waiting list. And a ***Reuters*** survey found 11 companies are spending a total of $2 billion on gene therapy production.

  This means smaller cell and gene therapy companies not building out their own facilities have few major places for production, and the FDA has warned that whoever produces the product for Phase I and II trials should be the producer for Phase III and commercialization or there is likely to be a lengthy approval delay. Remember, bridging studies don't work for cell and gene therapy, so moving manufacturing is not as easy as for drugs.

- CROSSROADS EXTREMITY SYSTEMS bought Surgical Frontiers' orthopedic implant portfolios, including Kator for Achilles tendon repair, OsteoPrecise for bone alignment in osteotomies and fusions, SpeedButton for reattachment of anatomic ligaments, and Metrics for the restoration of anatomic bone alignment and ligament function in ankle fractures and sprains.

- CYMABAY THERAPEUTICS' seladelpar – The company terminated all clinical programs with this PPARδ agonist after biopsies in a Phase IIb trial in non-alcoholic steatohepatitis (NASH) found "atypical" findings, including autoimmune hepatitis, in patients who had responded to the drug with either improvement or stabilization. Based on this, the company also halted a Phase II trial in primary sclerosing cholangitis and the Phase III ENHANCE trial in primary biliary cholangitis (PBC).

- Epilepsy – The ESETT trial, published in the ***New England Journal of Medicine***, compared three drugs used to treat status epilepticus – levetiracetam (UCB Pharmaceuticals' Keppra), fosphenytoin (Pfizer's Cerebyx), and generic valproate – in 384 patients with benzodiazepine-refractory status epilepticus and found them equally effective. All the drugs stopped ongoing seizures in ~50% of patients.

- EPITOPOIETIC RESEARCH CORP.'s Gliovac (ERC-1671) – The first U.S. patient to receive this investigational immunotherapy for recurrent glioblastoma under the Right to Try Act has died. However, another glioblastoma patient who received Gliovac has shown early signs of possible remission, though the durability of that remission is still unknown.

- FERRING PHARMACEUTICALS launched a new gene therapy subsidiary, FerGene, in partnership with Blackstone Life Sciences.

- Immunotherapy – Data, published in the ***Journal of the American Medical Association***, showed that prescriptions for Merck MSD's Keytruda (pembrolizumab), a PD-1 inhibitor, and Roche's Tecentriq (atezolizumab), a PD-L1 inhibitor, decreased rapidly (by ~40%) after the FDA changed the labels for metastatic bladder cancer, indicating that oncologists are staying up to date on these drugs.

- INCYTE's pemigatinib – The FDA accepted a new drug application (NDA) for this selective fibroblast growth factor receptor (FGFR) inhibitor for priority review as a treatment for previously treated, locally advanced/metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements. The PDUFA date is May 30, 2020.

- JOHNSON & JOHNSON's Ebola Zaire vaccine (adenovirus 26 vectored glycoprotein/MVA-BN-Filo vaccine) – Data from a Phase III trial using a 56-day interval between the two doses, presented at the American Society of Tropical Medicine and Hygiene (ASTMH) meeting in National Harbor MD, found this vaccine produced immune responses in two pediatric cohorts, with 98% of vaccinated kids having an immune response after the second dose. However, a Phase II trial also presented at the meeting showed that both a 28-day and a 56-day dosing interval produced similar responses.

- LA JOLLA PHARMACEUTICAL's LJPC-401 (synthetic human hepcidin) – After an interim analysis, the company halted the pivotal, ~100-patient LJ401-BT01 trial for iron overload in beta thalassemia (BT) due to lack of efficacy (no significant difference on the primary or key secondary endpoints vs. control). The company is reassessing the future of the drug.

- THE MEDICINES COMPANY – It's official: Novartis is buying The Medicines Company for $9.7 billion.

- **Opioids** – Four pharmas and two distributors – Amneal Pharmaceuticals, Johnson & Johnson, Mallinckrodt, Teva, AmerisourceBergen, and McKesson – are under federal criminal investigation for violating the Controlled Substances Act by failing to monitor distribution of their opioids.

- **PRECERA BIOSCIENCE's PrecisMed** – technology for analyzing blood to detect, measure, and evaluate >200 medications in the bloodstream of patients – was bought by **Phenomics Health**, a bioinformatics company.

- **SENSEONICS' Eversense** – A 945-patient study of this continuous glucose monitor (CGM) for Type 2 diabetics found the accuracy and CGM metrics were stable over multiple sensor insertion and removal cycles in real-world use.

- **TAKEDA's TAK-003**, a tetravalent dengue vaccine, met the primary endpoint in the Phase III TIDES trial in Latin America and Asia, published in the ***New England Journal of Medicine***, protecting children age 4-16 from virologically-confirmed dengue, with 80% efficacy at 12 months (two doses). However, data on patients at 18 months, presented at the American Society of Tropical Medicine and Hygiene (ASTMH) meeting, showed the efficacy was down to 73%, with hospitalizations down from 95% to 90% (a secondary endpoint).

- **USONA INSTITUTE's psilocybin** ("magic mushrooms") was granted breakthrough therapy designation by the FDA as a treatment for major depressive disorder.

- **Vaping update** – A report, published in the Centers for Disease Control and Prevention's (CDC's) ***Morbidity and Mortality Weekly Report***, confirms the suspicion that vitamin E acetate is the main culprit in the e-cigarette and vaping-associated lung injury (EVALI) cases. Minnesota law enforcement found that 11 of 12 Minnesota EVALI patients used illicit THC-containing products that contained vitamin E acetate. In addition, 20 THC-containing products seized during September 2019 contained vitamin E acetate, but none of the 10 products seized the previous year (before the EVALI outbreak) contained vitamin E acetate.

Very early research news

- **Oncology** – A study by Fox Chase Cancer Center researchers, published in the journal ***Cancer Discovery***, suggests that targeting epigenetic modifiers can "dial up or down" EGFR amplification and thereby modulate response to EGFR inhibitors in cancer patients. For example, KDM4A overexpression promotes copy gain, and the H3K27 methyltransferase EZH2 suppresses amplification. And the researchers showed that hypoxia and epidermal growth factor can directly promote EGFR amplification through modulation of the enzymes controlling EGFR copy gains. Basically, they showed that copy number is druggable by targeting the epigenetic factors involved. This could help develop ways to address resistance to an EGFR inhibitor.

NEWS IN BRIEF

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- **and NOVARTIS' Xolair (omalizumab).** The results of the ADAPT trial, published in ***JAMA Pediatrics***, showed that this anti-IgE is effective in treating children with severe atopic dermatitis, reducing severity and improving quality of life.

- **Risdiplam (RG-7916).** The FDA accepted an NDA and granted priority review to this oral SMN-2 splicing modifier as a treatment for spinal muscular atrophy (SMA). The PDUFA date is May 24, 2020.

- **Xofluza (baloxavir marboxil).** A study, published in ***Nature Microbiology***, suggested this anti-flu drug may be giving rise to resistant strains of influenza. The study found that nearly 25% of patients taking this drug had flu viruses with mutations in their genomes that made them less susceptible to the drug, and those mutations were not present before the patients took Xofluza.

REGULATORY NEWS

Regulatory tidbits

- **Device shortages.** The FDA's Center for Devices and Radiological Health (CDRH) plans to survey ~260 device makers quarterly to get data to monitor risk mitigation strategies in the event of device shortages.

- **Drug prices.** A Medbelle analysis compared the price for 13 prescription drugs in 50 countries around the world. The study found the U.S. pays 307% more than the global median for those drugs, making it the country with the most expensive drugs in the world, followed by Germany and the United Arab Emirates. The biggest price difference was for an ACE inhibitor for blood pressure control, AstraZeneca's Zestril (lisinopril), with the U.S. price 27-times the median.

- **Insulin.** The FDA issued draft guidance designed to make it easier to develop new forms of insulin.

- **Sterilization.** The FDA's CDRH announced new steps designed to encourage innovation in sterilization.
  - Recommending that labeling and instructions for use manuals be provided electronically where feasible and safe.

- Expedite approvals of certain changes, starting with a voluntary pilot project with two parts – one for device manufacturers and another for sterilization facilities.
- Allowing manufacturers to reference a master file instead of requiring a premarket approval (PMA) application supplement.

FDA approvals/clearances

- GLOBAL BLOOD THERAPEUTICS' Oxbryta (voxelotor) was granted accelerated approval to treat sickle cell disease in patients age ≥12. *This is the second sickle cell drug approved in the last month.*
- HEALTHLYTIX's RSI-MRI+, imaging software that uses an advanced diffusion technology and artificial intelligence to increase the visibility of restricted water in cancerous tissue, was granted 510(k) clearance for use in early diagnosis of prostate cancer.
- NANTHEALTH's Omics Core, a tumor-normal *in vitro* diagnostic test for measuring tumor mutation burden (TMB), was cleared for use.
- SANOFI's Toujeo (insulin glargine 300 U/mL) was granted expanded approval for use by Type 1 diabetic patients age ≥6.
- SIEMENS HEALTHINEERS' Somatom X.cite, a single-source computed tomography scanner, was cleared for use.
- TUSKER MEDICAL's Tula (Tubes Under Local Anesthesia) system was cleared for use in treating recurrent ear infections in adults and children.
- ZEBRA MEDICAL VISION's HealthCXR was granted 510(k) clearance for identification and triaging of pleural effusion in chest x-rays.

FDA recalls/warnings

- B. BRAUN MEDICAL's blood administration sets – The company voluntarily recalled 22 lots of these devices due to the potential for leakage at the joint between the filter and the tubing.
- Cannabidiol (CBD) – The FDA sent warning letters to 15 companies for illegally selling products containing cannabidiol. And the Agency issued a revised consumer update, warning that CBD may not be as safe as people think and noting that there are many unanswered questions and data gaps about CBD.
- GYNECOLOGY, REPRODUCTIVE ENDOCRINOLOGY AND FERTILITY INSTITUTE in San Juan, Puerto Rico, a fertility clinic, and its owner/medical director were ordered to immediately cease manufacturing due to "significant violations" of FDA regulations relating to donor screening and testing – and more.
- MEDTRONIC's MiniMed 600 – The company issued a letter warning patients that the reservoir on this insulin pump may become loose if a retainer ring breaks, leading to over- or under-dosing.
- ROCKWELL MEDICAL's Triferic (ferric pyrophosphate citrate) – The company received an untitled (warning) letter from the FDA's Office of Prescription Drug Promotion (OPDP) for failing to disclose risk information online and for making claims about this iron replacement product (delivered via hemodialysate) that suggest it is safer than IV iron replacement products.

European Regulatory News

- U.K. Dementia – Prime Minister Boris Johnson promised to double spending on dementia research (an extra $107 million/year) if his party is re-elected.
- CELLTRION's Remsima SC (infliximab) – a subcutaneous biosimilar formulation of Johnson & Johnson's Remicade – was approved by the European Medicines Agency (EMA) for treating eight autoimmune diseases, including rheumatoid arthritis.
- JOHNSON & JOHNSON's Darzalex (daratumumab) was granted expanded approval by the European Commission for use in a triple regimen – with Bristol-Myers Squibb/Celgene's Revlimid (lenalidomide) + dexamethasone – in newly diagnosed multiple myeloma patients unable to undergo an autologous stem cell transplant.
- Medical devices – The European Union gave reusable Class I devices and software a 4-year extension before they have to be fully compliant with the Medical Device Regulation (MDR).

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

- MERCK KGAA's Mavenclad (cladribine) – NICE dropped the requirement for patients to have a special MRI scan before being prescribed this multiple sclerosis drug.
- MERCK MSD's Keytruda (pembrolizumab) – In a draft decision, NICE recommended against use of this checkpoint inhibitor for bladder cancer, but the drug will remain available for that cancer through the Cancer Drugs Fund at least until January 2020 while NICE works on its final decision. The issue: not surprisingly cost-effectiveness.

Regulatory news from other countries

- ***Canada.*** Health Canada created a new Medical Device Directorate aimed at better responding to the medtech industry. It will focus on expanding Quality Management Systems, implementing ISO 9001, and improving post-market surveillance capacity for devices.
- ***China.*** MERCK MSD's Keytruda (pembrolizumab) was granted expanded approval by the National Medical Products Administration (NMPA) for use in combination with chemo-therapy (carboplatin + paclitaxel) as a first-line treatment for metastatic squamous non-small cell lung cancer (NSCLC).
- ***Japan.*** MYRIAD GENETICS' BRACAnalysis, for identifying breast cancer patients with BRCA1/2 mutations, was approved by the Ministry of Health, Labour, and Welfare (MHLW).

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 2	**Roche's Tecentriq** (atezolizumab) + chemotherapy for first-line treatment of metastatic non-squamous NSCLC	PDUFA date *Extended from September 2019*
December 3	Nomination of Stephen Hahn, MD, to be **FDA Commissioner**	Senate HELP Committee vote possible
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
December 9	Drug development for **non-alcoholic steatohepatitis** (NASH) and cholestatic liver diseases	FDA public workshop
December 10	**Correvio Pharma's Brinavess** (vernakalant), an antiarrhythmic for the rapid conversion of recent onset atrial fibrillation	FDA's Cardiovascular and Renal Drugs Advisory Committee
December 10	**Medication adherence**	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 13	**Horizon Therapeutics' teprotumumab** to treat active thyroid eye disease	FDA's Dermatologic and Ophthalmic Drugs Advisory Committee
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 *The date could be December 14*
December 16	Novel therapies for **stimulant use disorder**	FDA public workshop
December 22	**Bausch Health/Ortho Dermatologics' IDP-123** (tazarotene 0.045% lotion) for acne vulgaris	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 *Date not yet extended but 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*
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 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
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	**Esperion Therapeutics' bempedoic acid** monotherapy to treat hypercholesterolemia	PDUFA date
February 21	**Alder BioPharmaceuticals' eptinezumab** (ALD-403), a CGRP inhibitor for migraine	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**
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 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 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	**Bristol-Myers Squibb/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
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
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