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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NOTE: Subscribe to ***Trends-in-Medicine*** for coverage of the **American Society of Clinical Oncology** (ASCO) meeting in Chicago.

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

- ✓ BIOGEN's diroximel fumarate significantly improved radiological and clinical endpoints vs. Teva's Copaxone (glatiramer acetate) in an interim analysis of a Phase III trial in relapsing multiple sclerosis.
- ✓ BRAINSGATE – A large trial showed that using the company's sphenopalatine ganglion stimulation (SGS) system within 24 hours of the start of an acute ischemic stroke lowered disability levels at three months.
- ✓ NEWRON PHARMACEUTICALS' evenamide – The company is delaying its Phase II/III trials of this schizophrenia drug because of safety concerns raised by the FDA.

SHORT TAKES

- Absorbable hemostatic devices – The FDA's General and Plastic Surgery Devices Advisory Committee recommended that some absorbable (collagen) hemostatic devices be moved from Class III to Class II.
- AMARIN's Vascepa (icosapent ethyl) – The FDA accepted for priority review a supplementary new drug application (sNDA) for expanded approval of this omega-3 fish oil as a treatment to reduce residual cardiovascular risk in patients with statin-managed LDL cholesterol but persistent elevated triglycerides. The PDUFA date is September 28, 2019.
- AMICUS THERAPEUTICS expanded and extended its gene therapy research agreement with the Perelman School of Medicine at the University of Pennsylvania on lysosomal disorders and 12 additional rare diseases.
- APPLIED THERAPEUTICS' AT-007, an aldose reductase inhibitor treating galactosemia, was granted orphan drug status by the FDA.
- ASLAN PHARMACEUTICALS' ASLAN-004 – Aslan got the global rights to this investigational treatment, an anti-IL-13Rα1, for atopic dermatitis from **CLS**.
- BIOGEN's diroximel fumarate – Updated interim data from the ongoing single-arm, open-label Phase III EVOLVE-MS-1 trial in relapsing multiple sclerosis, presented at the Consortium of Multiple Sclerosis Centers (CMSC) meeting in Seattle, showed significant improvements in radiological and clinical endpoints at Year 1 vs. Teva's Copaxone (glatiramer acetate), with the adjusted annualized rate dropping 72% from baseline, and GD+ lesions dropping 64%. Only 0.7% of patients discontinued due to adverse gastrointestinal events.

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- BRAINSGATE – The results of the 1,078-patient ImpACT24-B trial of the company's sphenopalatine ganglion stimulation (SGS) system, presented at the European Stroke Organization Conference in Milan, Italy, and simultaneously published in ***The Lancet***, showed that patients who used this neurostimulator within 24 hours of the onset of an acute ischemic stroke had lower disability levels at three months post stroke, with no added side effect vs. sham.

- Cannabis – At an FDA public hearing on scientific data and information about products containing cannabis or cannabis/device compounds, Ned Sharpless, MD, acting FDA Commissioner, said there are many unanswered questions about cannabidiol (CBD) – safety, interactions, use in pregnancy or kids, long-term effects – and noting that there are "important reasons to generally prohibit putting drugs in the food supply," with CBD "no exception." Industry, academic, and consumer advocates all had ideas about how the FDA should regulate CBD – but all urged the FDA to set the rules soon.

- CARA THERAPEUTICS' Korsuva (difelikefalin, CR-845) – The company reported top-line data from the pivotal Phase III KALM-1 trial in severe pruritus (itching) among hemodialysis patients.

- CENTREXION THERAPEUTICS' CNTX-0290 – The exclusive global rights to this non-opioid pain drug for inflammatory, neuropathic, and mixed pain conditions were licensed to **Lilly**.

- CRYOPORT, a lifesciences logistics company, is buying **Cryogene**, which will give it a biostorage facility.

- EXACTECH bought **EPIC Extremity**, which makes foot and ankle screw and plating systems, joint and bone restoration products, and biologic solutions for knees, hips, and extremities.

- FIBROCELL Science's FCX-007, an investigational treatment for recessive dystrophic epidermolysis bullosa, a rare inherited skin disorder, was granted regenerative medicine advanced therapy (RMAT) status by the FDA.

- GALT PHARMACEUTICALS' Orphengesic Forte (orphenadrine citrate + caffeine + aspirin) – An sNDA for this non-opioid analgesic was granted priority review by the FDA. The PDUFA date is August 14, 2019.

- GLOBUS MEDICAL's ExcelsiusGPS, a robotic navigation system for spinal surgeries, showed a 99% success rate without placement-related postoperative return to the operating room.

- ICON is buying a majority of **MeDiNova Research**, which has research sites in Europe and Africa.

- IMARA's IMR-687, an investigational treatment for lowering sickling of red blood cells in sickle cell disease patients, was granted fast track status by the FDA.

- INOVIO PHARMACEUTICALS – **AstraZeneca** is scaling back its research agreement with Inovio.

- JUVENESCENCE launched **Souvien Therapeutics**, which will focus on development of drugs to treat neurodegenerative diseases using an epigenetic approach.

- Kidney dialysis – A study by Baylor College of Medicine researchers and colleagues, published in ***JAMA Network Open***, found that outcomes for kidney dialysis patients have been improving, but the declines in hospital days per patient-year and mortality rates improved slower in dialysis facilities that were acquired by larger organizations vs. those not acquired. An accompanying editorial said, "These findings raise concerns about whether patients realize significant benefits from consolidation in the dialysis industry."

- MALLINCKRODT is spinning off its specialty branded drugs portfolio, which will include Amitiza (lubiprostone), which treats chronic idiopathic constipation, into **Sonorant Therapeutics**.

- MEDIWOUND's NexoBrid – The company got an additional $21 million in funding from the Biomedical Advanced Research and Development Authority (BARDA) for the launch of this topical treatment for thermal burns.

- MESOBLAST's remestemcel-L – The company initiated a rolling submission of its biologics license application (BLA) for this treatment for pediatric acute graft-versus-host disease.

- NEWRON PHARMACEUTICALS' evenamide – The company said it is delaying its Phase II/III trials of this schizophrenia drug because of safety concerns raised by the FDA about this sodium channel blocker. The issue is central nervous system effects in rats and dogs, and the company will have to do additional preclinical testing.

- NOVARTIS' QMF-149 (indacaterol acetate + mometasone furoate) – This once-daily combination of a long-acting beta agonist (LABA) and a corticosteroid, delivered in a Breezhaler, met all the primary and key secondary endpoints in the 12-week, double-blind Phase III QUARTZ trial in asthma vs. mometasone (an inhaled steroid), with significant (and clinically meaningful) improvement in lung function.

- OVID THERAPEUTICS and TAKEDA's OV-935/TAK-935 – In a Phase Ib/IIa trial in developmental and epileptic encephalopathies, presented in a poster at the International Epilepsy Colloquium (IEC) in Lyon, France, this CH24H inhibitor had an acceptable safety and tolerability profile, with some initial evidence of a decrease in seizure frequency. The data also suggested that plasma 24HC may be a biomarker for assessing treatment outcomes and disease management.

- PHARMACEUTICAL PRODUCT DEVELOPMENT/EVIDERA is buying **Medimix International**, a global technology company with a real-world evidence service.

- PHILIPS/SPECTRANETICS' Stellarex – Three-year data from two European trials of this drug-coated balloon (DCB) showed it led to more patients maintaining blood flow through the diseased artery segments vs. a bare balloon, with no increased mortality from the paclitaxel-eluting balloon. In one, blood flow was maintained at Year 3 by 64.2% of Stellarex patients vs. 51% of bare balloon patients. A second trial found 67.5% of Stellarex patients maintained blood flow at Year 3 vs. 59.9% of bare balloon patients.

- RESOLUTION BIOSCIENCE's Resolution HRD, a liquid biopsy test for identifying sequence variations in homologous recombination deficiency-related genes, was granted breakthrough device designation by the FDA. It is a potential companion diagnostic for detecting gene deletions in cell-free DNA (cfDNA).

- Surgical staplers – The FDA revealed that there have been far more reports of harm and malfunction than previously released (>110,000) – because more than half the reports were non-public. The FDA's General and Plastic Surgery Devices Advisory Committee recommended that surgical staplers be moved from Class I devices to Class II.

- TAKE SOLUTIONS/NAVITAS LIFE SCIENCES bought **KAI Research**, a contract research organization (CRO).

- VERTEX PHARMACEUTICALS' VX-445 (elexacaftor + tezacaftor + ivacaftor) – This is the 3-drug combination that the company plans to submit to the FDA as its newest treatment for cystic fibrosis.

Animal health news

- NORBROOK LABORATORIES is recalling 34 lots of its veterinary injectable drug products as a precautionary measure because sterility cannot be assured.

NEWS IN BRIEF

BAYER

- **Aliqopa (copanlisib)**, a PI3K inhibitor, was granted breakthrough therapy designation by the FDA as a treatment for relapsed marginal zone lymphoma patients who had ≥2 prior systemic therapies.

- Is collaborating with **Roche/Foundation Medicine** on development of a next-generation sequencing (NGS)-based companion diagnostic for multiple investigational cancer therapies, starting with Vitrakvi (larotrectinib) in solid tumors with TRK fusion mutations.

BIOMARIN's valoctocogene roxaparvovec ("valrox")

- The company provided an update of a Phase II trial of this gene therapy for hemophilia A, showing a significant drop in blood rates over three years.

- However, the company also reported that Factor VIII levels decreased in that Phase II trial, raising questions about the durability of this treatment (from a mean of 36.4 IU/dL at the end of Year 2 to 32.7 IU/dL at the end of Year 3 with the 6e13 vg/kg dose).

- In interim results from an ongoing Phase III trial, Factor VIII levels at 6 months were less than at the same time period in the Phase II trial. However, the company said it met the criteria for accelerated FDA approval.

REGULATORY NEWS

Regulatory tidbits

- Drug prices. A World Health Organization (WHO) committee approved a draft resolution urging member states to share information on net drug prices with the public and support distribution of information about clinical trial costs. However, the resolution did not suggest requiring drugmakers to disclose research and development costs.

- FDA accelerated approval. Two studies, published in ***JAMA Internal Medicine***, question the FDA's use of the accelerated approval pathway and surrogate endpoints in approving new cancer therapies.

  - One study found that of the 93 cancer drugs granted accelerated approval from 1992-2017, only 20% of the postmarket confirmatory trials demonstrated an improvement in overall survival.

  - The other study looked at drugs approved on response rate. For the 59 cancer drugs approved from 2006-2018,

the median response rate was 41% and a complete response rate of 6%.

- One accompanying editorial noted, "These studies remind us that most new cancer drugs are of marginal benefit at best, despite their immense cost."
- A second editorial suggested there is no good reason the FDA should "rely so heavily on accelerated approval using response rate or other unreliable surrogate endpoints."

- Insulin. The governor of Colorado signed a bill that limits the cost of insulin to patients at ≤$100/month, effective January 1, 2020. The Colorado attorney general also is required to investigate the recent spike in insulin prices and submit the findings by November 2020.
- Opioids. The FDA is seeking public comment on its new authority to require that certain immediate-release (IR) opioids be distributed in fixed-quantity, unit-of-use blister packages.

FDA approvals/clearances

- ALLERGAN and GEDEON RICHTER's Vraylar (cariprazine), an antipsychotic, was granted expanded approval to treat bipolar depression in adults.
- ASTELLAS' Xospata (gilteritinib) was granted expanded labeling to include a claim for overall survival improvement vs. salvage chemotherapy in acute myeloid leukemia.
- CELGENE's Revlimid (lenalidomide) was granted expanded approval for use in combination with Roche's Rituxan (rituximab) to treat adults with previously-treated follicular lymphoma or marginal zone lymphoma (MZL).
- MEDIVIS' SurgicalAR, an augmented reality platform for use in surgical procedures, was granted 510(k) clearance.
- MEDTRONIC's SelectSite C304-HIS, a deflectable catheter system for His-bundle pacing procedures, was cleared for use.
- THERANICA BIO-ELECTRONICS' Nerivio Migra, a non-invasive neuromodulation device that uses smartphone-controlled electronic pulses for treating acute migraines in adults who don't have chronic migraine, was cleared for use.

FDA recalls/warnings

- HERITAGE PHARMACEUTICALS' amikacin injection and prochlorperazine edisylate injection, manufactured by **Emcure Pharmaceuticals**, were recalled after failing a sterility test.
- R3 STEM CELL received an untitled letter advising the company that its stem cell products, which are used at >50 affiliated sites to treat a variety of conditions (e.g., Lyme disease, Parkinson's disease), are not approved by the FDA.
- TERUMO's SOLOPATH, a balloon expandable transfemoral system with a re-collapsible balloon access system, was recalled (Class I) because of tip dislodgements.

European Regulatory News

- ADVANCED ACCELERATOR APPLICATIONS' LysaKare (arginine + lysine) – The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended approval to protect the kidneys against radiation during radioactive therapy with lutetium (^{177}Lu) oxodotreotide.
- EMMAUS MEDICAL EUROPE's Xyndari (glutamine) – CHMP recommended against approval to treat sickle cell disease.
- MITSUBISHI TANABE PHARMA's Radicava (edaravone) – The marketing authorization application to treat amyotrophic lateral sclerosis was withdrawn after CHMP said a new 12-month, placebo-controlled trial is needed to demonstrate efficacy.
- NEMAURA MEDICAL's SugarBEAT, a non-invasive patch continuous glucose monitor (CGM) for diabetics, was granted a CE Mark.
- UNIVAR's Cufence (trientine dihydrochloride) – CHMP recommended approval of this treatment for Wilson's disease.
- ZENTIVA's Ambrisentan Zentiva (ambrisentan) – The marketing authorization application to treat pulmonary arterial hypertension was withdrawn.

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

- MERCK MSD's Prevymis (letermovir) – NICE reversed itself and recommended approval of this antiviral to prevent cytomegalovirus reactivation and disease after an allogeneic hematopoietic stem cell transplant (HSCT) in adults who are seropositive for CMV – after the company offered a discount on the price.

Regulatory news from other countries

- ***Canada.*** ALLERGAN's Biocell – Health Canada suspended the company's license for these textured breast implants over concerns about an increased cancer risk. Then, Allergan announced it will recall its textured breast implants in Canada and will halt further sales there.
- ***China.*** JIANGSU HENGRUI's camrelizumab, a PD-1 inhibitor, was approved, making it the fifth checkpoint inhibitor approved in China.
- ***Japan.*** TRANSENTERIX's Senhance, a robot-assisted surgical device, was granted Shonin approval by the Ministry of Health, Labor, and Welfare for use in general surgery, urology, gynecology, and some thoracic procedures.
- ***South Korea.*** The European Commission approved South Korea for safe inspections and regulations of active drug ingredients.

2019 FDA Advisory Committees and Other Regulatory Dates of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
tba	**Sedor Pharmaceuticals' IM/IV Captisol-Enabled Fosphenytoin** (fosphenytoin sodium and sulfobutylether beta-cyclodextrin sodium for injection) to treat generalized tonic-clonic status epilepticus and seizures during neurosurgery	PDUFA date of March 22 missed *No announcement yet*
June 3	**Merck MSD's Zerbaxa** (ceftolozane and tazobactam) for hospital-acquired bacterial pneumonia (HABP)	PDUFA date
June 6	**Global Alliance for TB Drug Development's pretomanid** to treat resistant tuberculosis in combination with bedaquiline + linezolid	FDA' s Antimicrobial Drugs Advisory Committee
June 10	**Xeris Pharmaceuticals' liquid glucagon autoinjector** for severe hypoglycemia	PDUFA date
June 10	**Merck MSD's Keytruda** (pembrolizumab) for first-line treatment, as monotherapy or in combination with chemotherapy, for recurrent/metastatic squamous cell head and neck cancer	PDUFA date
June 11-12	Discussion of clinical efficacy and safety of the **higher range of opioid analgesic dosing** (both higher strength products and higher daily doses) in the outpatient setting	FDA's Anesthetic and Analgesic Drug Products Advisory Committee meeting jointly with the Drug Safety and Risk Management Advisory Committee
June 17	**Merck MSD's Keytruda** (pembrolizumab) for monotherapy of ≥3-line advanced SCLC	PDUFA date
June 19-20	Discussion of safety of peripheral use of **paclitaxel-eluting stents and balloons**	FDA's Circulatory System Devices Advisory Committee
June 20	**AM:** Discussion of reauthorization of Relevant Pediatric Molecular Target List **PM:** Discussion of potential pediatric development plans for 2 adult cancer products – Oncoceutics' ONC-201 and OncoImmune's CD24Fc	FDA's Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)
June 20	**Merck MSD's Keytruda** (pembrolizumab) for first-line treatment, in combination with Pfizer's Inlyta (axitinib) for advanced renal cell carcinoma	PDUFA date
June 21	**Glenmark Pharmaceuticals' Ryaltris** (olopatadine + mometasone furoate) for seasonal allergic rhinitis	PDUFA date ***Extended from March 21***
June 21	**Agios' Tibsovo** (ivosidenib) for front-line IDH1+ acute myeloid leukemia (AML)	PDUFA date
June 23	**Palatin Technologies' Vyleesi** (bremelanotide, PT-141) for hypoactive sexual desire	PDUFA date *Extended by the FDA from March 23*
June 25	**Acer Therapeutics' Edsivo** (celiprolol) to treat vascular Ehlers-Danlos syndrome	PDUFA date
June 26	**Sanofi** and **Regeneron Pharmaceuticals' Dupixent** (dupilumab), expanded approval to treat severe chronic rhinosinusitis with nasal polyps	PDUFA date
June 27	**Celgene's Revlimid** (lenalidomide) for relapsed/refractory follicular lymphoma	PDUFA date
June 28	**Alexion Pharmaceuticals' Soliris** (eculizumab) – expanded approval to include neuromyelitis optica spectrum disorder in patients with anti-aquaporin-4 antibodies	PDUFA date
July 6	**Karyopharm Therapeutics' selinexor** for relapsed/refractory multiple myeloma	PDUFA date *Extended by FDA from April 6*
July 15-16	Discussion of ***in vitro* diagnostics**	FDA public workshop
July 16	Discussion of alternative approaches in clinical investigations of new animal drugs	FDA public workshop by the Center for Veterinary Medicine
July 17	Second of 3 public meetings on electronic submission of adverse event reports to FAERS	FDA public meeting
August 3	**Daiichi Sankyo's pexidartinib** for treatment of tenosynovial giant cell tumor (TGCT)	PDUFA date
August 8	Discussion of development of **antiviral drugs** to treat adenoviral infection in immunocompromised patients	FDA public workshop
August 12	Discussion of individualized **drug dosing** in the real-world	FDA public workshop
August 14	**Galt Pharmaceuticals' Orphengesic Forte** (orphenadrine citrate + caffeine + aspirin), a non-opioid painkiller	PDUFA date
August 18	**Roche's entrectinib** for NTRK fusion-positive solid tumors and ROS1+ metastatic non-small cell lung cancer (NSCLC)	PDUFA date

2019 FDA Advisory Committees and Other Regulatory Dates of Interest – continued (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
August 19	**Roche's polatuzumab vedotin** for relapsed/refractory DLBCL	PDUFA date
August 25	**Daiichi Sanyo's quizartinib** for relapsed/refractory FLT3-ITD AML	PDUFA date *Extended from May 25 by the FDA*
August 29	**Nektar Therapeutics/Inheris Biopharma's NKTR-181** for low back pain	PDUFA date *Extended by the FDA from May 28*
September tba	**Lilly's Emgality** (galcanezumab-gnlm), expanded approval of this CGRP inhibitor to treat episodic cluster headaches	PDUFA date
September 3	**Celgene's fedratinib**, a JAK2 inhibitor for myelofibrosis	PDUFA date
September 17	Standards for future **opioid therapy approvals**	FDA public meeting
September 27	**Intra-Cellular Therapies' lumateperone** for schizophrenia	PDUFA date
September 28	**Amarin's Vascepa** (icosapent ethyl) – expanded approval to reduce cardiovascular risk in statin-managed patients with high triglycerides	PDUFA date
November 4	**Roche's Xofluza** (baloxavir marboxil), expanded use as a single-dose treatment for patients at high risk of flu complications	PDUFA date
November 30	**Aquestive Therapeutics' Exservan** (riluzole oral film) for ALS	PDUFA date
2020 FDA Advisory Committees and Other Regulatory Meetings and Events		
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