TRENDS-in-MEDICINE

October 11, 2020

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: The Covid-19 section starts on Page 5.

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

- ✓ President Trump appears recovered from Covid-19.
- ✓ ALKERMES' ALKS-3831 (olanzapine/samidorphan) – An FDA advisory committee gave thumbs *up* to this atypical antipsychotic combination.
- ✓ AMAG PHARMACEUTICALS' Makena (hydroxyprogesterone caproate injection) – The FDA is moving to withdraw this preterm birth reduction drug from the market.
- ✓ ARBOR PHARMACEUTICALS' AR-19 (amphetamine sulfate immediate-release) – An FDA advisory committee gave a thumbs *down* to this abuse-deterrent ADHD drug.
- ✓ BRISTOL-MYERS SQUIBB is buying MyoKardia.
- ✓ INTERCEPT PHARMACEUTICALS' Ocaliva (obeticholic acid) – The FDA is evaluating whether this PBC drug causes liver injury.
- ✓ Y-MABS THERAPEUTICS' omburtamab – The FDA issued a refusal to file letter for this treatment for pediatric CNS/leptomeningeal metastasis from neuroblastoma.
- ✓ **Positive trial news:**
  - ABBVIE's Kaletra (lopinavir + ritonavir) + interferon beta-1b in MERS.
  - AMGEN, CYTOKINETICS, and SERVIER's omecamtiv mecarbil – in HFrEF.
  - AXOVANT GENE THERAPIES' AXO-Lenti-PD – in Parkinson's disease.
  - BRISTOL-MYERS SQUIBB's Opdivo (nivolumab) + chemotherapy – in resectable NSCLC before surgery.
  - GILEAD SCIENCES' Biktarvy (bictegravir + emtricitabine + tenofovir alafenamide) – in long-term use in HIV and in HIV patients with an M184V/I mutation.
  - LILLY's Reyvow (lasmiditan) – in new results in migraine.
  - MERCK MSD and BAYER's vericiguat – in HFrEF.
  - PFIZER and OPKO HEALTH's somatrogon – in pediatric growth hormone deficiency.
  - VIIV HEALTHCARE's Dovato (dolutegravir + lamivudine) – in HIV.
- ✓ **Negative trial news:**
  - BRISTOL-MYERS SQUIBB's Opdivo (nivolumab) + Yervoy (ipilimumab) – in Stage IIIb/c/d or Stage IV melanoma.
  - PFIZER's Ibrance (palbociclib) – in HR+/HER2-negative early breast cancer with residual invasive disease after neoadjuvant chemotherapy.
- ■ SANTHERA's Puldysa (idebenone) – in DMD.

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SHORT TAKES

- **ABBVIE's Kaletra (lopinavir + ritonavir)** – The results of the 95-patient MIRACLE trial, published in the ***New England Journal of Medicine***, found that the combination of interferon beta-1b + this HIV drug reduced mortality vs. placebo (28% vs. 44% at Day 90) in hospitalized patients with laboratory-confirmed Middle East Respiratory Syndrome (MERS).

- **ABFERO PHARMACEUTICALS' SP-420** – A pharmacokinetic study in 12 healthy volunteers showed that the planned doses of this iron chelator are in the right range for treating transfusional iron overload.

- **ALKERMES' ALKS-3831 (olanzapine/samidorphan)** – The FDA's Psychopharmacologic Drugs Advisory Committee, meeting jointly and virtually with the Drug Safety and Risk Management Advisory Committee, voted 16-1 that this atypical antipsychotic combination effectively mitigates the weight gain that occurs with olanzapine alone, 13 to 3 (with 1 abstention) that it is safe, and 11 to 6 that the label warnings are sufficient.

- **AMAG PHARMACEUTICALS' Makena (hydroxyprogesterone caproate injection)** – The FDA's Center for Drug Evaluation and Research (CDER) recommended that this drug for reducing the risk of preterm birth should be ***withdrawn*** from the market because the required postmarketing study failed to show the drug reduced the risk of preterm birth or to improve the health of babies born to women with a history of unexplained preterm birth. *Remember, Covis recently announced it is buying AMAG.*

- **AMGEN, CYTOKINETICS, and SERVIER's omecamtiv mecarbil (CK-1827452)** – In top-line results from the 8,256-patient, global Phase III GALACTIC-HF trial in heart failure with reduced ejection fraction (HFrEF), this myosin activator met the primary endpoint, significantly reducing the composite of time to cardiovascular death or heart failure events vs. placebo, but it missed a key secondary endpoint, failing to reduce time to cardiovascular death by itself.

- **ARBOR PHARMACEUTICALS' AR-19 (amphetamine sulfate immediate-release)** – The FDA's Psychopharmacologic Drugs Advisory Committee, meeting jointly (and *virtually)* with the Drug Safety and Risk Management Advisory Committee, rejected this abuse-deterrent formulated treatment for attention-deficit/hyperactivity disorder (ADHD), voting unanimously that the risks outweigh the benefits. The panel also voted 19-2 (with 2 abstentions) that the safety of the drug was not clear.

- **ARROWHEAD PHARMACEUTICALS' ARO-AAT** – **Takeda** is partnering on this investigational RNAi treatment for alpha-1 antitrypsin-associated liver disease (AATLD).

- **ATCC Federal Solutions** got a contract worth up to $250 million from the Biomedical Advanced Research and Development Authority (BARDA) to provide storage and logistics for specimen handling, including Covid-19 studies.

- **Atrial fibrillation** – Last year U.K. and Korean researchers published data in the ***European Heart Journal*** showing that atrial fibrillation was linked to an increased risk of dementia, even in people who had not suffered a stroke. Now, the same researchers have published another study in the ***European Heart Journal*** which found that AFib patients who had catheter ablation had a 27% reduced risk of developing dementia vs. AFib patients who were treated with medication only.

- **AVROBIO's AVR-RD-05** – The exclusive global rights to this lentiviral gene therapy for Hunter syndrome (mucopolysaccharidosis type II, MPS II) was licensed from the University of Manchester, U.K.

- **AXOVANT GENE THERAPIES' AXO-Lenti-PD** – Six-month follow-up data from the second cohort of patients in the open-label, dose-escalation Phase II SUNRISE-PD trial in Parkinson's disease showed a >20-point improvement in the UPDRS OFF score in motor function, with meaningful improvement in quality of life measures. A sham controlled trial, EXPLORE-PD, will start in 2021.

- **BIOGEN** is partnering with **Scribe Therapeutics** to develop and commercialize CRISPR-based therapies to treat amyotrophic lateral sclerosis (ALS).

- **Breast implants** – A retrospective study by South Korean researchers, published in ***JAMA Surgery***, found that textured breast implants used for post-mastectomy reconstruction have a small but significant increased risk of breast cancer recurrence vs. smooth implants. The 5-year disease-free survival was 93.3% for women with textured implants and 97.8% for those with a smooth implant.

- **ENTERPRISE THERAPEUTICS**'portfolio of TMEM16A potentiators for treating cystic fibrosis was acquired by **Roche**.

- **FERRING PHARMACEUTICALS' Noccdurna (desmopressin acetate)** was exclusively licensed in the U.S. to **Antares Pharma** to treat nocturia due to nocturnal polyuria.

- **Flu vaccine** – A poll of 1,000 American adults by the National Foundation for Infectious Diseases found that only 59% of respondents plan to get a flu vaccine this year.

- **Hypothyroidism** – An investigation of 10 years of real-world evidence by FDA and academic scientists, published in ***JAMA Network Open***, found that patients taking levothyroxine benefit equally from generic and brand-name drugs.

- **IMMUNOGEN's IMGN-632**, a CD123-targeted antibody-drug conjugate (ADC), was granted breakthrough therapy designation by the FDA as a treatment for relapsed/refractory blastic plasmacytoid dendritic cell neoplasm.

- **INTERCEPT PHARMACEUTICALS' Ocaliva (obeticholic acid)** – The FDA is evaluating whether this treatment for primary biliary cholangitis (PBC) causes liver injury, and that investigation began before the FDA issued a complete response letter for Ocaliva in non-alcoholic steatohepatitis (NASH). The investigation could take as long as a year to conclude.

- **INVITAE** bought **ArcherDx**.

- **IOVANCE BIOTHERAPEUTICS' lifileucel (LN-144)** – The company said it has not reached an agreement with the FDA on the potency assays needed for defining this tumor-infiltrating lymphocyte (TIL) therapy in metastatic melanoma, and this will delay a biologics license application (BLA) submission to the Agency until some time in 2021.

- **MERCK KGAA's M-6495** (formerly ALX-1141), an anti-ADAMTS5 nanobody for osteoarthritis, was exclusively licensed to **Novartis**.

- **MERCK MSD and BAYER's vericiguat** – An analysis of 5,040 patients from the VICTORIA trial, presented at the Heart Failure Society of America (HFSA) virtual meeting, showed that this oral soluble guanylate cyclase stimulator was more effective than placebo in patients with heart failure with reduced ejection fraction (HFrEF), regardless of background therapy used. However, beta blocker patients who were taking ≥50% of their dose had a significantly greater benefit from vericiguat than those taking <50%.

- **MODERNA's mRNA-1172** – **Merck MSD** returned all rights to Moderna to this respiratory syncytial virus (RSV) vaccine, which Merck had been co-developing with Moderna. Merck will focus instead on its RSV antibody program.

- **Neuromodulation** – A 15-patient study, published in ***Bioelectronic Medicine***, suggests that spinal cord stimulation could treat both the motor and non-motor symptoms (e.g., pain) in Parkinson's disease patients.

- **POLAREAN IMAGING** submitted a new drug application (NDA) to the FDA for its inhaled hyperpolarised ^{129}Xenon gas, a drug-device combination, for use in lung MRIs without the need for ionizing radiation.

- **PROTEOMICS** is collaborating with the QMIR Berghofer Medical Research Institute in Australia on development of a blood test for esophageal cancer.

- **RITE AID** is buying **Bartell Drugs**.

- **ROCHE/GENENTECH** is partnering with **Imbio** on development of quantitative imaging diagnostics for lung diseases.

- **SANTHERA PHARMACEUTICALS' Puldysa (idebenone)** – An interim analysis of the Phase III SIDEROS trial determined that this synthetic analogue of coenzyme Q10 was unlikely to meet the primary endpoint, FVC%p at 18 months, in Duchenne muscular dystrophy (DMD) patients in respiratory decline and who were receiving a glucocorticoid. At the recommendation of the data safety monitoring board, the company discontinued the trial for futility.

- **SARTORIUS** is buying **BIA Separations**, a purification specialist.

- **SEATTLE GENETICS** changed its name to **Seagen**.

- **STADA ARZNEIMITTEL** bought **Lobsor Pharmaceuticals**.

- **STERIS** is buying **Key Surgical**.

- **STRYKER** sold its Stryker Performance Solutions' (SPS) business and segments of its SPS health system orthopedic analytics subscription business to Healthcare Outcomes Performance Company (**HOPCo**).

- **Telemedicine** – A study, published in ***JAMA Network Open***, found that in 2Q20 in-office primary care visits in the U.S. dropped ~21% (from 120-130 million to ~99 million per quarter in 2018 and 2019). On the other hand, telemedicine consults increased 30-fold to >35 million in 2Q20. However, blood pressure screenings dropped 50%, and cholesterol testing was down 37%.

- **TRANSMEDICS' TransMedics Organ Care System (OCS) Heart** – The review of this normotheral heart transplant storage system by the FDA's Circulatory System Devices Advisory Committee, which was scheduled for October 7, 2020, was postponed indefinitely by the FDA.

- **VIIV HEALTHCARE's Dovato (dolutegravir + lamivudine)** – The 3-year results of the Phase III GEMINI-1 and GEMINI-2 trials in treatment-naïve HIV-1, presented at the virtual HIV Glasgow 2020 congress, showed that this 2-drug regimen for HIV continued to be non-inferior to a 3-drug regimen of dolutegravir + 2 nucleoside reverse transcriptase inhibitors (NRTIs) – Gilead Sciences' Viread (tenofovir disoproxil fumarate) + emtricitabine. However, Dovato had fewer drug-related adverse events.

- **Y-MABS THERAPEUTICS' omburtamab** – The FDA issued a refusal to file letter for the BLA for this treatment for pediatric patients with CNS/leptomeningeal metastasis from neuroblastoma, citing issues with the chemistry, manufacturing, and control (CMC) data and requesting additional clinical data.

- **ZOSANO PHARMA's Qtrypta (zolmitriptan transdermal microneedle system, M207)** – The FDA sent a discipline review letter (DRL) to the company about this treatment for acute migraine, raising concerns about the clinical pharmacology and variations in drug lots. As a result, it is unlikely that the FDA will make a decision on the 505(b)(2) application by the PDUFA date of October 20, 2020.

NEWS IN BRIEF

BRISTOL-MYERS SQUIBB

- Is buying **MyoKardia** for ~$13 billion, which will give it mavacamten for treating hypertrophic cardiomyopathy.

- **Opdivo (nivolumab) + Yervoy (ipilimumab).** This PD-1/CTLA4 inhibitor combination failed to significantly improve recurrence-free survival in all comers in the Phase III CheckMate-915 trial in Stage IIIb/c/d or Stage IV melanoma. This means the trial missed both primary endpoints – survival in all comers and survival in patients with tumors expressing <1% PD-L1.

- **Opdivo (nivolumab) + chemotherapy** met the primary endpoint in the Phase III CheckMate-816 trial in resectable non-small cell lung cancer (NSCLC) – before surgery – significantly improving pathologic complete response vs. chemotherapy alone.

GILEAD SCIENCES' Biktarvy (bictegravir + emtricitabine + tenofovir alafenamide)

In data presented at the virtual HIV Glasgow 2020 meeting:

- Long-term results showed that HIV patients who switched to this once-daily combination HIV drug from a boosted protease inhibitor-based regimen maintained viral suppression out to 156 weeks.

- A pooled analysis of 6 switching studies found that 98% of HIV patients with an M184V/I mutation who switched to Biktarvy maintained their virologic suppression, with no treatment resistance emerging.

LILLY

Two studies, presented at the virtual Migraine Trust International Symposium, showed:

- **Reyvow (lasmiditan).** In new results from the 1,471-patient Phase III CENTURION trial, this serotonin 5-HT_{1F} receptor agonist met a co-primary endpoint, showing superiority on pain freedom at 2 hours post-dose vs. placebo in at least 2 of 3 attacks – a 10%-20% improvement in therapeutic gain over placebo.

- **PROs.** An analysis of 586 U.S. patients in the global OVERCOME survey of patient-reported outcomes in migraine found that:
  - 79.2% of migraine patients taking a CGRP inhibitor to prevent migraine believed their migraines have been "better" since starting the drug.
  - 62.6% also used an additional migraine medication with the CGRP antibody.

PFIZER

- **and OPKO HEALTH's somatrogon**, a long-acting (once-weekly) human growth hormone, met the primary endpoint in an open-label, crossover Phase III trial in children with growth hormone deficiency, significantly improved treatment burden vs. Pfizer's daily Genotropin (somatropin), with a life interference score of 8.63 at Week 12 vs. 24.13 for somatropin.

- **Ibrance (palbociclib).** This CDK4/6 inhibitor missed the primary endpoint in the Phase III PENELOPE-B trial, failing to significantly improve disease-free survival in women with HR+/HER2-negative early breast cancer with residual invasive disease after neoadjuvant chemotherapy.

Pharma survey

A survey of >550 pharmaceutical industry CEOs being presented at the CPhI Festival of Pharma found:

- For the first time, the overall aggregated confidence score – the CPhI Pharma Index – decreased 0.86% across all nations.
- India has the most growth potential.
- China's growth potential decreased – and the decrease was the largest in the history of this annual survey – but it is expected to bounce back in 2021.
- Italy's API manufacturing increased, putting it in 5th place, putting only Germany ahead of it in Europe.
- Italy and India were the only countries to have an improved CPhI Pharma Index score in 2020.

- Overall, the industry has weathered the pandemic well.
- 84% said they are looking for new supply side partners.
- Pharma CEOs are divided on the idea of doing more domestic production, with 48% saying that would be desirable, 37% saying that would be too disruptive, and 15% saying flatly that it would be a bad idea.

U.S. Presidential election

A survey of 130 healthcare executives conducted in mid-September by Advis, a healthcare consisting firm, found:

- 46% believe a second-term Trump/Pence administration would be better for the future of U.S. healthcare, with 41% saying a Biden/Harris administration would be better, and 13% undecided.
- In Trump/Pence administration second term:
  - ✓ 75% expect further dismantling of the Affordable Care Act.
  - ✓ 56% expect increased efforts to control prescription drug costs.
- In a Biden/Harris administration:
  - ✓ 73% expect to see a form of Medicare-for-all with opt-out options for commercial plans.
  - ✓ 69% expect strengthening of the Affordable Care Act.

COVID-19 WEEKLY HIGHLIGHTS

- As of October 11, there have been:
  - 37 million cases of Covid-19 worldwide with 21% (7.8 million) of those in the U.S.
  - 1 million people have died from Covid-19 worldwide, including more than 200,000 in the U.S. (20% of the worldwide cases)
  - Per 100,000 people, the ***per capita*** death rate from Covid-19 is 0.23 worldwide, 65.1 in the U.S., which compares to 71.5 in the U.K., 58.9 in Sweden, and 11.6 in Germany.
  - The ***per capita*** death rate per 100,000 people in select U.S. states ranges from a low of 28.8 in Washington to a high of 161.6 in New Jersey.
- President Trump was released from Walter Reed Medical Center and appears to be his old self. His doctor says he no longer can transmit the virus but didn't say when the President last had a negative test.
- Emergency use authorizations (EUAs). The FDA issued guidance on EUAs for Covid-19 vaccines. Among the key requirements:
  - Chemistry, manufacturing, and controls information.
  - Non-clinical and clinical data.
  - Regulatory and administrative information.
  - The review will be done on a case-by-case basis, considering the target population, the characteristics of the product, the preclinical and human clinical trial data, and the totality of the available scientific evidence.
  - The FDA's Vaccines and Related Biological Products Advisory Committee will hold an open panel meeting on the vaccine prior to any EUA being issued. And the FDA

Worldwide Covid-19 Statistics as of October 11, 2020

Country	Population	Cases	Deaths	Case Fatality rate	Per Capita Fatality Rate (per 100,000)
Worldwide	7,577 million	**37,378,245**	**1,074,985**	**2.9%**	**0.23**
U.S.	330 million	**7,759,183**	**214,761**	**2.8%**	**65.1**
Spain	47 million	861,112	32,929	3.8%	70.1
Italy	60 million	354,950	36,166	10.2%	60.3
France	67 million	732,434	32,601	4.5%	48.7
U.K.	67 million	606,446	42,915	7.9%	71.5
Germany	83 million	326,306	9,621	2.9%	11.6
Sweden	10 million	98,451	5,894	6.0%	58.9
Canada	38 million	184,403	9,666	5.2%	25.4
China	**1,386 million**	**104,516**	**6,052**	**5.8%**	**0.44**
India	1,353 million	7,053,806	108,334	1.5%	8.0
Mexico	126 million	814,328	83,642	10.3%	66.4
Russia	145 million	1,291,687	22,471	1.7%	15.5
Brazil	210 million	5,082,637	150,198	3.0%	71.5

U.S. Covid-19 Statistics as of October 11, 2020

Country	Population	Cases	Deaths	Case Fatality rate	Per Capita Fatality Rate (per 100,000)
Arizona	7.3 million	220,671	5,759	2.6%	78.9
California	39.5 million	846,579	16,564	2.0%	41.9
Florida	**21.5 million**	**712,884**	**15,552**	**2.2%**	**72.3**
Georgia	10.6 million	331,409	7,416	2.2%	70.0
Illinois	12.6 million	319,150	8,984	2.8%	71.3
Louisiana	4.6 million	172,059	5,462	3.2%	118.7
Massachusetts	6.9 million	186,168	9,388	5.0%	136.1
Michigan	10 million	134,656	7,219	5.4%	72.2
New Jersey	8.9 million	213,628	14,386	6.7%	161.6
New York	**19.4 million**	**474,286**	**25,574**	**5.4%**	**131.8**
North Carolina	10.5 million	224,727	3,735	1.7%	35.6
Texas	29 million	792,478	16,557	2.1%	57.1
Washington	7.6 million	93,035	2,190	2.4%	28.8
Total of these states	**188.4 million**	**4,721,730**	**138,786**	**2.5%**	**73.7**

will "rapidly schedule" any panel meeting after there is a BLA submission or EUA request.

■ Testing. **Abbott's ID Now** – The interim results of a post-EUA study of this rapid Covid-19 test found 93.3% sensitivity and 98.4% specificity.

■ Transmission. The Centers for Disease Control and Prevention (CDC) finally admitted that there is airborne transmission of SARS-CoV-2, though still saying that is not the main method of transmission. And the CDC said when airborne transmission occurs it is generally in poorly ventilated and enclosed spaces, often involving activities that cause heavier breathing (e.g., singing or exercise).

■ Treatments

- **Gilead Sciences' Veklury (remdesivir)**
  - ✓ The final results of the ACTT-1 trial of this antiviral, published in the ***New England Journal of Medicine***, showed superiority to placebo in shortening time to recovery in hospitalized Covid-19 patients with lower respiratory tract infection.
  - ✓ The National Institutes of Health is starting a 500-patient, global Phase III trial of remdesivir + convalescent plasma in Covid-19 patients with symptoms for ≤12 days without life-threatening organ dysfunction/failure, with the help of Emergent BioSolutions, Grifols, and Takeda (with CSL Behring).
- **Hydroxychloroquine** – The results of the open-label, 4,716-patient RECOVERY trial, published in the ***New England Journal of Medicine***, missed the primary endpoint, failing to improve 28-day mortality vs. placebo, and mortality was actually numerically worse with hydroxychloroquine (27.0% vs. 25.0%).
- **Jazz Pharmaceuticals' Luvox (fluvoxamine) and generics** – A 152-outpatient study suggested that this SSRI antidepressant may be an effective treatment for mild Covid-19.
- **Lilly's**
  - ✓ **bamlanivimab (LY-CoV-555) + etesevimab (LY-CoV-016, Junshi Biosciences' JS-016)** – In interim data from the Phase II BLAZE-1 trial of 112-patients with mild-to-moderate Covid-19, this 2-antibody combination reduced virus levels, hospitalizations (0.9% vs. 5.8%), and emergency room visits. Lilly applied to the FDA for a second EUA for this combination.
  - ✓ **Olumiant (baricitinib)**, a JAK inhibitor, + remdesivir met the primary endpoint in an NIAID-sponsored trial.
- **Pfizer's Zithromax (azithromycin) and generics** – The results of the COALITION-II trial, published in ***The Lancet***, showed no benefit to adding this antibiotic to hydroxychloroquine in hospitalized Covid-19 patients.
- **Regeneron Pharmaceuticals and Roche's REGN-COV2** – President Trump gave a lot of credit to his quick recovery from Covid-19 to this antibody, and Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), said there is a "reasonably good chance" that it helped the President. Regeneron also offered the antibody to former Vice President Joe Biden and his team, but he didn't say if Biden took the company up on the offer.

■ Vaccines

- **Allele Biotechnology and Pharmaceuticals** sued Regeneron Pharmaceuticals, Pfizer, and BioNTech, accusing each of these companies of using its mNeonGreen fluorescent protein without permission to develop Covid-19 therapies/vaccines.
- **Chinese Academy of Medical Sciences' *inactivated* SARS-CoV-2 vaccine** – Phase I data suggested the vaccine is safe and triggers an immune response. Neutralizing antibody titers dropped from Day 14 to Day 28, but the importance of that was not discussed. In preprint data on ***medRxiv***, a 192-patient Phase I trial of three doses, using two dosing schedules, showed it was safe and tolerable. Side effects were mostly injection site pain/redness or slight fatigue.
- **Pfizer and BioNTech's BNT-162b2** – The European Medicines Agency (EMA) started a rolling review of this Covid-19 vaccine.
- **Transparency.** Peter Marks, MD, director of the FDA's Center for Biologics Evaluation and Research (CBER), suggested that vaccine makers could be required by the FDA to disclose serious safety issues if the Agency doesn't think they are being sufficiently transparent.
- **U.K.** The head of the U.K. vaccine task force said that the government plans to inoculate <50% of the people in that country, with the focus on healthcare workers, care workers, and the "vulnerable." No one under age 18 will get it.

REGULATORY NEWS

Regulatory tidbits

■ Antibiotics.

■ Covid-19 – The House Subcommittee on Economic and Consumer Policy sent letters to the FDA and the CDC seeking documents and information about the role of the White House in determining Covid-19-related policy and public health messages.

- **Diuretics** – University of Kentucky researchers filed a petition with the FDA seeking the recall of one lot each of Mylan and Hikma's versions of acetazolamide, an injectable diuretic, after they found high impurity levels in tested lots.
- **FDA review times** – Jeffrey Shuren, MD, director of the FDA's Center for Devices and Radiological Health (CDRH), speaking at the Virtual MedTech Conference, sponsored by AdvaMed, said that FDA reviewers have been keeping up with the heavy workload of Covid-19 drugs and devices on top of their already busy schedules, but the staff are getting tired and that is starting to slow the processing of non-Covid-19-related products, including premarket authorizations and 510(k) clearances. "We are starting to see our performance on some of our submissions starting to slip, and it really is a canary in the coal mine," Dr. Shuren said.
- **Lab-developed tests (LDTs)** – The FDA said it will no longer review emergency use authorization (EUA) submissions for lab-developed SARS-CoV-2 tests and will not require premarket review of LDTs.
- **Orphan drug research** – The FDA awarded six new clinical trial research grants totaling >$16 million over the next 4 years through the Congressionally-funded Orphan Products Grants Program designed to enhance development of medical products for rare diseases. The drugs are:
  - **Ability Pharma's ABTL-0812** – $1.9 million to the University of Cincinnati for a Phase I/II trial in pancreatic cancer
  - **Acucela's emixustat hydrochloride** – $1.6 million for a Phase III trial to treat Stargardt disease
  - **Bristol-Myers Squibb/Celgene's oral 5-azacitidine + romidepsin** – $3.2 million to the University of Virginia for a Phase II trial in treating peripheral T-cell lymphoma
  - **CAR T** – $3.1 million to State University of New York Stony Brook for a Phase I trial of CD4-redirected CAR T therapy to treat CD4+ T cell neoplasms
  - **Genta's Ganite (gallium nitrate)** – $3 million to Seattle Children's Hospital for a Phase Ib trial in cystic fibrosis patients with non-tuberculosis mycobacterium
  - **Johnson & Johnson's Stelara (ustekinumab)** – $3.5 million to Fred Hutchinson Cancer Research Center for a Phase II trial in prevention of graft-versus-host disease

FDA approvals

- **ABBVIE and IRONWOOD PHARMACEUTICALS' Linzess (linaclotide)** was granted expanded approval to add "bloating" and "discomfort" to the label for this irritable bowel syndrome with constipation (IBS-C) drug.
- **ATRILITY MEDICAL's AtriAmp**, an atrial arrhythmia monitor, was granted 510(k) clearance.
- **BECTON DICKINSON's FACSLyric Flow Cytometer**, an integrated cell analyzer, was granted 510(k) clearance.
- **CHEMBIO DIAGNOSTICS' DPP HIV-Syphilis System**, which includes the DPP Micro Reader optical analyzer and a multiplex single-use test, was granted premarket approval.
- **HAEMONETICS' NexSys PCS system**, with Persona technology that customizes plasma collection based on a donor's body composition, was granted 510(k) clearance.
- **JOHNSON & JOHNSON/BIOSENSE WEBSTER's Thermocool SmartTouch SF**, an ablation catheter for treating persistent atrial fibrillation, was cleared for use.
- **MEDTRONIC's Resolute Onyx**, a drug-eluting cardiac stent, was granted expanded labeling for use with only one month of dual antiplatelet therapy (DAPT) in patients with a high bleeding risk.
- **ORTHOFIX MEDICAL's Firebird** was granted expanded clearance to include a 3D-printed joint screw.
- **SENTIAR's CommandEP**, a holographic cardiac guidance system, was granted 510(k) clearance.

FDA recalls/warnings

- **Covid-19** – The FDA and the Federal Trade Commission jointly sent warning letters for the sale of fraudulent Covid-19-related herbal products to Griffo Botanicals and Prairie Dawn Herbs.
- **BATTELLE MEMORIAL INSTITUTE's Battelle Critical Care Decontamination System** – Battelle received a warning letter for failing to comply with regulatory requirements for medical devices with an EUA, specifically failing to report adverse events related to this respirator decontamination device.
- **MARKSANS PHARMA's metformin extended-release** – The recall of this diabetes drug was expanded to include an additional 76 lots due to possible contamination with NDMA.
- **NALPROPION PHARMACEUTICALS' Contrave (naltrexone + bupropion)** – The company received a warning letter from the Office of Prescription Drug Promotions for "false or misleading claims" about this obesity drug.
- **SUN PHARMACEUTICAL INDUSTRIES' Riomet ER (metformin extended-release)** – One lot was recalled due to possible contamination with NDMA.

European Regulatory News

- CURVEBEAM's HiRise, a CT imaging system for the lower extremities, was granted a CE Mark.
- PERKINELMER's EONIS, an assay for screening newborns for severe combined immunodeficiency, X-linked agamma-globulinemia, and spinal muscular atrophy, was granted a CE Mark.

Regulatory news from other countries

- *Canada.* BRISTOL-MYERS SQUIBB's Zeposia (ozanimod) – Health Canada approved this oral S1P receptor modulator to treat relapsing-remitting multiple sclerosis.

2020 FDA Advisory Committees and Other Regulatory Dates of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
October 7	**TransMedics' TransMedics Organ Care System** (OCS) **Heart** – normothermic heart transplant transport	FDA's Circulatory System Devices Advisory Committee virtual meeting **Postponed indefinitely by the FDA**
October 13	Patient-focused drug development for **systemic sclerosis**	FDA virtual public meeting
October 13	Respirators and other **PPE** for healthcare personnel use	FDA webcast
October 13-14	Update and **strategic plan** for 2021-2025 for National Antimicrobial Resistance Monitoring System (NARMS)	FDA's Center for Veterinary Medicine webcast
October 14	Enhancing development of **radiopharmaceuticals and radiological devices**	FDA-NRC virtual workshop
October 14	Coronavirus test development and validation	FDA virtual Town Hall
October 14	Update on the **Sentinel Initiative** for medical product device safety	FDA and Duke University virtual public workshop
October 15	Final guidance on recognition and withdrawal of **voluntary consensus standards**	FDA webcast
October 15-16	New approaches for an integrated non-clinical/clinical **QT/proarrhythmic risk assessment**	FDA webcast
October 18	**Roche's Herceptin** (trastuzumab) **+ Perjeta** (pertuzumab) – a fixed dose combination to treat HER2+ breast cancer	PDUFA date
October 19	Digital Health Center of Excellence **Listening Session #1**	FDA webcast
October 19-20	Updates on ongoing research to address challenges of **generic drug-device combination products**	FDA and Drug Information Agency (DIA) Generic Drug-Device Combination Products *virtual* Conference
October 22	**Covid-19 vaccines** general discussion	FDA's Vaccines and Related Biological Products Advisory Committee virtual meeting
October 22	**Artificial intelligence** and machine learning in medical devices	FDA's Patient Engagement Advisory Committee virtual meeting
October 22	Conversation on Cancer: Building connections toward **Native American** trial participants	FDA webcast
October 22-23	Pediatric **dose selection**	FDA virtual public workshop
October 24	**Spectrum Pharmaceuticals' Rolontis** (eflapegrastim) for treating chemotherapy-induced neutropenia	PDUFA date
October 25	**Regeneron Pharmaceuticals' REGN-EB3** for Ebola	PDUFA date
October 27	Antimicrobial drugs to treat **gonorrhea**	FDA virtual public workshop *Postponed from August 21*
October 27	**Medical device user fee** amendments for fiscal years 2023-2027	FDA virtual public meeting
October 27	**Neovasc's Neovasc Reducer System** for treating refractory angina pectoris	FDA's Circulatory System Devices Advisory Committee virtual meeting
October 30	Integrated assessment of **marketing applications**	FDA virtual public workshop
November 2	Sentinel Initiative on **maternal health and pregnancy**	FDA virtual training session
November 2	**Olas Pharma's Hydexor** (hydrocodone + acetaminophen + promethazine) for acute post-operative pain	FDA's Anesthetic and Analgesic Drug Products Advisory Committee virtual joint meeting with the Drug Safety and Risk Management Advisory Committee
November 6	**Biogen and Eisai's aducanumab** in Alzheimer's disease	FDA's Peripheral and Central Nervous System Drugs Advisory Committee virtual meeting
November 12	Digital Health Center of Excellence **Listening Session #2**	FDA webcast
November 13	**Orthopedic device-related infections**	FDA virtual public workshop
November 15	**Alkermes' ALKS-3831** (olanzapine + samidorphan) for bipolar I disorder and schizophrenia	PDUFA date
November 16	**Bristol-Myers Squibb/Celgene/Juno Therapeutics' lisocabtagene maraleucel** (JCAR-017, liso-cel) for DLBCL	PDUFA date *Postponed from August 17*
November 16	Ranking of **antimicrobial drugs** by importance in human medicine	FDA virtual public meeting by the FDA's Center for Veterinary Medicine
November 17	**Safety of medical devices**	FDA virtual public meeting
November 19	**CBD and other cannabinoids** – sex and gender differences in use and response	FDA's Office of Women's Health virtual Scientific Conference
November 19	Reauthorization of the **Biosimilar User Fee Act** (BsUFA) for FY2023-2027	FDA virtual public meeting
November 20	**Eiger BioPharmaceuticals' Zokinvy** (lonafarnib) for progeria and progeroid laminopathies	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**
November 25	**Revance Therapeutics' daxibotulinumtoxinA** for moderate-to-severe glabellar lines	PDUFA date
November 27	**Rhythm Pharmaceuticals' setmelanotide** for pro-opiomelanocortin deficiency obesity and leptin receptor deficiency obesity	PDUFA date
December tba	**Pfizer and Lilly's tanezumab** to treat moderate-to-severe osteoarthritis pain	PDUFA date
December 3	**BioCryst Pharmaceuticals' Orladeyo** (berotralstat, BCX-7353) for hereditary angioedema attacks	PDUFA date
December 3	**Alnylam Pharmaceuticals' lumasiran** for primary hyperoxaluria type 1	PDUFA date
December 20	**FibroGen and AstraZeneca's roxadustat** for anemia of chronic kidney disease	PDUFA date
December 20	**Myovant Sciences' Relumina** (relugolix) for advanced prostate cancer	PDUFA date
December 26	**Sumitomo Dainippon Pharma/Urovant Sciences' vibegron** for overactive bladder	PDUFA date
December 30	**Almirall and Athenex's tirbanibulin** (KX2-391, KX-01) for actinic keratosis	PDUFA date
2021		
January 20	**Merck MSD and Bayer's vericiguat** in HFrEF	PDUFA date
January 26	Non-clinical immunogenicity assessment of **generic peptide products**	FDA virtual public workshop
January 27	**Protalix BioTherapeutics and Chiesi's pegunigalsidase alfa** (PRX-102) for Fabry disease	PDUFA date
February 11	**Regeneron Pharmaceuticals' evinacumab** in severe homozygous familial hypercholesterolemia (HoFH)	PDUFA date
February 15	**G1 Therapeutics' trilaciclib** for small cell lung cancer	PDUFA date
February 28	**Roche's Gavreto** (pralsetinib) in RET-mutated medullary thyroid cancer	PDUFA date
March 7	**Biogen and Eisai's aducanumab** for Alzheimer's disease	PDUFA date
March 27	**Bristol-Myers Squibb and bluebird bio's idecabtagene vicleucel** (ide-cel, bb-2121), a CAR T therapy for relapsed/refractory multiple myeloma	PDUFA date