TRENDS-in-MEDICINE

September 27, 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: This is a two-week issue. We apologize that circumstances prevented publication last week. The Covid-19 section starts on Page 5. Subscribe to ***Trends-in-Medicine*** for coverage of two virtual conferences: **ESMO 2020** and the **European Association for the Study of Diabetes (EASD)**.

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

- ✓ AQUESTIVE THERAPEUTICS' Libervant (diazepam) was rejected by the FDA as a treatment for seizure clusters.
- ✓ ASTRAZENECA's AZD-1222 – This Covid-19 vaccine trial hold because of a case of transverse myelitis was lifted in the U.K. but not yet in the U.S.
- ✓ ILLUMINA is buying **Grail** for $8 billion.
- ✓ MALLINCKRODT's terlipressin was rejected by the FDA as a treatment for hepatorenal syndrome type 1.
- ✓ MERCK MSD invested $1 billion in **Seattle Genetics**, getting the rights to two breast cancer drugs and more.
- ✓ NOVARTIS' Zolgensma (onasemnogene abeparvovec-xioi) – The FDA is requiring another trial in children age 2-5 with spinal muscular atrophy (SMA) before approval.
- ✓ Ulcerative colitis – ICER found 8 targeted therapies to be unreasonably expensive.
- ✓ VERTEX PHARMACEUTICALS' Trikafta (elexacaftor + tezacaftor + ivacaftor) – ICER found this cystic fibrosis drug has the best efficacy data but is too expensive.
- ✓ **Positive trial results:**
  - ACHIEVE LIFE SCIENCES' cytisinicline – in smoking cessation.
  - BIOMARIN PHARMACEUTICAL's vosoritide – in pediatric achondroplasia.
  - BOEHRINGER INGELHEIM's BI-425809 – in schizophrenia.
  - CALA HEALTH's Cala Trio – in essential tremor.
  - FREQUENCY THERAPEUTICS' FX-322 – in chronic sensorineural hearing loss.
  - MARINUS PHARMACEUTICALS' ganaxolone – in CDKL5 deficiency disorder.
  - NOVARTIS' Beovu (brolucizumab-dbll) in diabetic macular edema (DME) and Tafinlar (dabrafenib) in combination with Mekinist (trametinib) in melanoma.
  - OTSUKA's Jynarque (tolvaptan) – in decompensated liver cirrhosis.
  - TYME TECHNOLOGIES' racemetyrosine (SM-88) – in recurrent prostate cancer.
- ✓ **Negative trial results:**
  - ROCHE and AC IMMUNE's semorinemab – in early Alzheimer's disease.
  - VACCINEX's pepinemab – in Huntington's disease.

SHORT TAKES

- ACHIEVE LIFE SCIENCES' cytisinicline – In the 679-patient head-to-head RAUORA trial in smoking cessation among indigenous New Zealanders (and their extended families), presented at the Society for Research on Nicotine and Tobacco European (SRNT-E) virtual conference, this 5-HT3 receptor agonist met the primary endpoint, showing non-inferiority to **Pfizer's Chantix** (varenicline) but with less nausea and vivid dreams.

- AQUESTIVE THERAPEUTICS' Libervant (diazepam buccal film) – The FDA rejected this benzodiazepine as a treatment for seizure clusters, issuing a complete response letter (CRL) which cited issues with dosing and protocol deviations. The company believes the issues can be resolved quickly.

- ASTRAZENECA is buying **Dogma Therapeutics**' preclinical oral PCSK9 inhibitor program for treating familial hypercholesterolemia.

- BAYER exclusively licensed ERSO – a small molecule activator of the Unfolded Protein Response (UPR) – in preclinical development to treat metastatic ER+ breast cancer, from **Systems Oncology**.

- BIOMARIN PHARMACEUTICAL's vosoritide – The results of a 121-patient, 52-week Phase III pediatric achondroplasia trial, presented at the American Society for Bone and Mineral Research (ASBMR) virtual meeting, showed that daily injection of this C-type natriuretic peptide analog significantly improved average growth velocity vs. placebo.

- BIOMÉRIEUX's Nephroclear CCL14, a kidney injury diagnostic test, will be exclusively distributed in the U.S. and Europe by Baxter.

- CALA HEALTH's Cala Trio – In a 44-patient, 3-month, at-home study of this neuromodulation device, worn twice daily on the wrist, 57% of patients with essential tremor had a ≥2-fold reduction in tremors. When used during the most severe tremors, 90% of patients had a ≥2-fold reduction in tremors.

- CTI CLINICAL TRIAL AND CONSULTING SERVICES purchased **Clinart**, a full-service contract research organization (CRO) based in the Middle East.

- Cystic fibrosis – The Institute for Clinical and Economic Review (ICER) released its final report on the cost-effectiveness of cystic fibrosis drugs. Among the findings: that **Vertex Pharmaceuticals' Trikafta** (elexacaftor + tezacaftor + ivacaftor), which costs $311,000/year, has the best efficacy data but is priced too high. ICER chief medical officer David Rind, MD, bemoaned the price, saying, "The manufacturer has leveraged its monopoly to set a price costing many millions of dollars over the lifetime of an average patient." To make Trikafta cost-effective, the price would have to be reduced to $67,900-$85,500/year.

- FREQUENCY THERAPEUTICS' FX-322 – The results of a long-term extension study of a subset of patients from a 90-day Phase I/II trial found that patients with chronic sensorineural hearing loss (SNHL) who had significant improvements in key measures of hearing at 90 days with a single injection of this drug – a combination of small molecules that activate inner ear progenitor cells – sustained those improvements out to 21 months.

- GILEAD SCIENCES' magrolimab, an anti-CD47, was granted breakthrough therapy designation as a treatment for newly-diagnosed myelodysplastic syndrome (MDS).

- ILLUMINA is buying **Grail** for $8 billion.

- LEGEND BIOTECH CEO Frank Zhang, PhD, is under house arrest in China, and the CFO has taken over. Chinese authorities are investigating Zhang for possible customs violations at his prior company, GenScript Biotech, not for any alleged Legend wrongdoing.

- MALLINCKRODT's terlipressin, a vasopressin analog, was rejected as a treatment for hepatorenal syndrome type 1 (HRS-1) by the FDA, which issued a complete response letter (CRL) saying more data are needed to support a positive risk:benefit profile. Remember an FDA advisory committee was split 8-7 in favor of approval of this drug.

- MARINUS PHARMACEUTICALS' ganaxolone met the primary endpoint in the Phase III Marigold trial, significantly reducing 28-day major motor seizure frequency vs. placebo in CDKL5 deficiency disorder (CDD), a rare form of genetic epilepsy – -32.2% vs. -4.0%.

- MEDTRONIC's TYRX – The results of the WRAP-IT trial found this absorbable antibacterial envelope for use in patients receiving a cardiac implantable electronic device who are at increased risk of infection is cost-effective.

- NEO MEDICAL is partnering with **Orthofix** on development of a cervical platform with single-use, sterile-packed procedure solutions.

- NOVUS THERAPEUTICS bought **Anelixis Therapeutics**, which gives it a next-generation anti-CD40 for treating organ and cellular transplantation, autoimmune diseases, and neurodegenerative diseases.

- ORPHAZYME's arimoclomol – The FDA accepted a new drug application (NDA) for this heat-shock protein amplifier for treating Niemann-Pick disease Type C (NPC) and granted it priority review.

- OTSUKA's Jynarque (tolvaptan) – A 100-patient retrospective study, published in Japan's ***Journal of Gastroenterology***, found that this vasopressin receptor antagonist improved outcomes in patients with decompensated liver cirrhosis and water retention.

- PURDUE PHARMA's OxyContin (oxycodone extended-release, abuse-deterrent formulation) – The FDA's Anesthetic and Analgesic Drug Products Advisory Committee, meeting jointly with the Drug Safety and Risk Management Advisory Committee, voted 20-7 (with 1 abstention) that the abuse-deterrent formulation (ADF) of OxyContin "meaningfully reduced" abuse by snorting or injection, but did not agree that it lowered overall abuse risk.

- QIAGEN bought **NeuMoDx Molecular**, a diagnostics instrument company.

- SAMSUNG expanded it partnership on **PharmAbcine's PMC-403**, an investigational treatment for neovascular disorders.

- SAREPTA THERAPEUTICS was sued by the University of Pennsylvania and **RegenxBio**, who charged that Sarepta's gene therapy programs, including its Duchenne muscular dystrophy drugs, infringe on a patent originally owned by the University of Pennsylvania and now held by RegenxBio.

- SIRTEX MEDICAL invested in **Nanospectra Biosciences**, which will give it access to AuroLase, an ultra-focal gold nanoparticle prostate cancer tissue ablation treatment, outside the U.S.

- SKYLINEDX is partnering with the University of California San Diego School of Medicine and Imperial College London on development of a diagnostic test to detect Kawasaki disease early.

- TAKEDA is collaborating with **Foundation Medicine** on development of tissue- and blood-based companion diagnostics for use with Alunbrig (brigatinib), an ALK inhibitor, and mobocertinib, an EGFR2 TKI.

- TYME TECHNOLOGIES' racemetyrosine (SM-88) – The final results of a Phase II trial in non-metastatic recurrent prostate cancer were published in the journal ***Investigational New Drugs***, showed good disease control while maintaining quality of life. SM-88 also may delay the need for androgen deprivation therapy (ADT).

- VACCINEX's pepinemab missed both co-primary endpoints in the Phase II SIGNAL trial in Huntington's disease, failing to significantly beat placebo on two cognitive measures on the CGIC.

- VIVA BIOTECH is buying **SYNthesis**, a Hong Kong-based preclinical CRO.

NEWS IN BRIEF

BAUSCH HEALTH

- Is buying **Allegro Ophthalmics**' ophthalmological assets.

- **ETON PHARMACEUTICALS' ketotifen (EM-100).** The FDA still has not made a decision on this preservative-free eye drop for treating ocular itching associated with allergic conjunctivitis. The original PDUFA date was August 10, but the date was extended by the FDA to September 15. However, there is still no word from the FDA.

BOEHRINGER INGELHEIM

- BI-425809, a Gly-T1 inhibitor, improved cognition in the double-blind Phase II Study 1346.9 trial in stable schizophrenics.

- **and LILLY's Jardiance (empagliflozin)**, an SGLT2 inhibitor, was granted fast track status by the FDA as a treatment to prevent hospitalization due to heart failure and to lower the risk of all-cause mortality in adults with and without diabetes who have already had a myocardial infarction.

- Is collaborating with **Mirati Therapeutics** on a KRAS-KRAS combination – a study of BI-1701963, a SOS1::pan-KRAS inhibitor, in combination with MRTX-849, a KRAS G12C selective inhibitor – in lung and colorectal cancer.

BRISTOL-MYERS SQUIBB

- **and bluebird bio's idecabtagene vicleucel (ide-cel, bb-2121).** The FDA accepted the biologics license application (BLA) for this CAR T therapy for treating relapsed/refractory multiple myeloma and granted it priority review. The PDUFA date is March 27, 2021.

- **CELGENE's Revlimid (lenalidomide).** The company settled its patent dispute with Dr. Reddy's Laboratories. The agreement means Dr. Reddy's can start selling a limited volume of generic lenalidomide – a multiple myeloma treatment – in the U.S. in March 2022 and without limitation as of January 31, 2026.

- Exercised its option for an exclusive worldwide license to **Obsidian Therapeutics**' cytoDrive technology (CD40L therapy) for use in developing cell and gene therapies.

CRISPR

A survey of 368 drug discovery and therapeutic scientists about CRISPR by Synthego found:

- Only 50% of respondents were satisfied with their CRISPR editing results.
- 75% still outsource their gene editing.
- Nearly 50% of respondents in both commercial and non-commercial institutions said they were "not comfortable" handling large-scale experiments (>100 samples simultaneously).

MERCK MSD

- Made a $1 billion investment in **Seattle Genetics' ladiratuzumab vedotin**, an antibody-drug conjugate (ADC) targeting LIV-1 for breast cancer, with plans to develop it as both monotherapy and in combination with Merck's Keytruda (pembrolizumab), a PD-1 inhibitor.
- Exclusively licensed Tukysa (tucatinib), a TKI for HER2+ cancers, for use outside the U.S., Canada, and Europe, from **Seattle Genetics**.

MODERNA

- Is collaborating with **Vertex Pharmaceuticals** on discovery and optimization of lipid nanoparticles (LNPs) for treating cystic fibrosis.
- Is partnering with **Chiesi** on development of mRNA treatments for pulmonary arterial hypertension (PAH).

NOVARTIS

- **Beovu (brolucizumab-dbll)** met the primary endpoint in the Phase III KITE trial, showing non-inferiority to Regeneron Pharmaceuticals and Sanofi's Eylea (aflibercept) in change in best-corrected visual acuity (BCVA) at Week 52 in patients with diabetic macular edema (DME). Beovu also showed superiority to Eylea on a key secondary endpoint, change in central subfield thickness.
- **Gilenya (fingolimod).** An online survey of 99 neurologists by Spherix Global Insights found that this S1P receptor modulator remains the U.S. favorite for treating multiple sclerosis (MS), but prescription for Bristol-Myers Squibb's Zeposia (ozanimod), another S1P receptor modulator, is picking up.
- **Tafinlar (dabrafenib).** The full results of the Phase III COMBI-AD trial, published in the ***New England Journal of Medicine***, showed that 52% of stage III BRAF-V600E mutated melanoma patients taking this BRAF inhibitor, in combination with Mekinist (trametinib), a MEK inhibitor, were alive and relapse-free at 5 years vs. 36% of placebo patients. Median relapse-free survival was not reached with the Tafinlar/Mekinist combination vs. 16.6 months for placebo.
- **Zolgensma (onasemnogene abeparvovec-xioi).** The FDA asked the company to test spinal infusions of this gene therapy for spinal muscular atrophy (SMA) in children age 2-5 before approval, which likely will delay approval until at least 2023. This does not affect the current approval for children age ≤2.

ROCHE

- Is buying **Inflazome**, which is developing NLRP3 inhibitors for use in treating diseases such as Parkinson's disease, Alzheimer's disease, inflammatory bowel disease, arthritis, and more.
- **and AC IMMUNE's semorinemab**, an anti-tau antibody, missed a co-primary endpoint in the Phase II TAURIEL trial in patients with early Alzheimer's disease, failing to reduce cognitive decline on the CDR-SB test vs. placebo. The data are not in yet on the other primary endpoint, tau reduction in the brain. Semorinemab also missed two key secondary endpoints: ADAS-Cog13 and ADCS-ADL.

Ulcerative colitis and targeted immune modulators – The ICER view

The Institute for Clinical and Economic Review (ICER) reviewed eight drugs for treating ulcerative colitis, concluding all are unreasonably expensive, suggesting the prices need to come down:

- AbbVie's Humira (adalimumab), a TNF inhibitor
- Johnson & Johnson/Janssen's Simponi (golimumab), a TNF inhibitor; Stelara (ustekinumab), an anti-IL-12/23 inhibitor; and Remicade (infliximab), a TNF inhibitor.
- Merck MSD's Renflexis (infliximab-abda), a biosimilar of Remicade
- Pfizer's Inflectra (infliximab-dyyb) – another Remicade biosimilar – and Xeljanz (tofacitinib), a JAK inhibitor
- Takeda's Entyvio (vedolizumab), an integrin inhibitor

ICER concluded:

- The cost-effectiveness per quality-adjusted life year (QALY)
  - Ranged in biologic-naïve patients from $186,000 for Pfizer's generic infliximab to $1,870,000 for Humira.

- Ranged in biologic-experienced patients from $495,000 with Xeljanz to $1,885,000 for Humira.

- The incremental cost of these drugs vs. convention treatment was modest.
- Few patients remain on the initial drug longer than a year.
- Humira, Simponi, Stelara, and EntyAvio are unlikely to be cost-effective in biologic-naïve patients.
- Remicade and infliximab biosimilars had the best cost-effectiveness in biologic-naïve patients but were still greater than the $150,000 cost per QALY threshold.
- None of the drugs were cost-effective vs. conventional treatment in biologic-experienced patients, but Xeljanz had greater QALYs at a lower cost than Humira.

COVID-19 WEEKLY HIGHLIGHTS

- CDC – The Centers for Disease Control and Prevention (CDC) reversed itself twice in the last 2 weeks:
  - The CDC said that people without symptoms who had been exposed to someone positive for Covid-19 may not need a test, but then it issued new guidance that people who have been in close contact with an infected person "need a test."
  - The CDC posted information which said that Covid-19 aerosolizes and can be spread at distances >6 feet but then pulled that information, saying it was a draft that was posted by mistake.
- Elective procedures – Medical claims data from IQVIA showed that compared to pre-Covid levels:
  - Elective procedures for the last week of August were down 17%, slightly worse than the previous week (when it was -15%).
  - In-person physician visits were down ~24% in the first week of September (vs. -14% the previous week).
- Lockdowns
  - **Florida.** Gov. Ron DeSantis lifted all restrictions on businesses across the state.
  - **Pennsylvania.** A federal judge overturned the governor's Covid-19 orders that closed businesses and limited gatherings, saying that, though they were issued "with good intentions," they violated the First and Fourteenth Amendments so were unconstitutional.
- PPE
  - Researchers at ECRI, a not-for-profit organization that advises hospitals, government organizations, and others on safety, found that 60%-70% of the KN95 masks imported from China do not meet minimum U.S standards, failing to filter 95% of aerosol particulates. The really bad news is that some U.S. hospitals have been ordering these masks. ECRI tests nearly 200 masks.
  - Researchers at Henry Ford Health System and the University of Michigan reported in the ***International Journal of Infectious Diseases*** that certain N95 respirators (3M 1860 and Moldex 1511 masks) can be effectively and safely decontaminated (from SARS-CoV-2) for reuse with ultraviolet-C (UV-C) light, the same light used in phototherapy to treat rare skin diseases.
- Testing
  - The FDA published comparative performance data on 58 molecular coronavirus tests that got an emergency use authorization (EUA), comparing them to an FDA reference panel.
  - The CDC and the European Union's Joint Research Centre (JRC) plan to work with **Siemens Healthineers** on standardizing international antibody tests for Covid-19.
  - A study, published in ***JAMA Network Open***, found that a routine blood test for red cell distribution width could be used to determine Covid-19 patients at risk for severe illness and death. Patients with levels above normal were nearly three times as likely to die from the disease.
- Travel
  - On September 14, 2020, the U.S. government removed requirements for directing all flights carrying airline passengers arriving from, or recently had a presence in, certain countries – China, Iran, the Schengen region of Europe, the United Kingdom, Ireland, and Brazil – to land at one of 15 designated airports and halted enhanced entry health screening for those passengers.
  - The airline industry called for Covid-19 antigen tests before all international flights, so negative travelers won't have to be quarantined when they reach their destination.
  - United Airlines said it plans to start providing 15-minute Covid-19 tests for passengers headed to Hawaii.
- Treatment
  - ALLOVIR's ALVR-109 – An investigational new drug application (IND) was granted by the FDA for this off-the-shelf T cell therapy for Covid-19, clearing the way for a proof-of-concept trial to start.

- **FUJIFILM and DR. REDDY'S LABORATORIES' Avigan (favipiravir)**, an antiviral, met the primary endpoint in a 156-patient Phase III trial in Covid-19 patients with non-severe pneumonia, shortening recovery time vs. placebo (11.9 days vs.14.7 days).
- **Hydroxychloroquine** – A 649-patient European study, published in ***EP Europace***, found that short-term use of hydroxychloroquine (200 mg BID with or without a 400 mg BID loading dose the first day) was not associated with lethal heart arrhythmia in Covid-19 patients who are risk-assessed prior to receiving the drug. The study was not designed to test the efficacy of hydroxychloroquine in Covid-19 patients (with either early or late disease).
- **LILLY and INCYTE's Olumiant (baricitinib)** – The companies said they will seek an EUA from the FDA for this JAK inhibitor as a treatment for Covid-19 in combination with Gilead Sciences' Veklury (remdesivir), based on the results of a trial run by the National Institute of Allergy and Infectious Diseases (NIAID) which found that Covid-19 patients on the combination recovered quicker than patients on remdesivir alone.
- **ROCHE's Actemra (tocilizumab)** – This anti-IL-6 may have utility in Covid-19 after all. After first failing to show a benefit in a Covid-19 trial, tocilizumab met the primary endpoint in a second Phase III trial, EMPACTA, with patients with Covid-19-associated pneumonia who got tocilizumab 44% less likely to progress to mechanical ventilation or death vs. placebo (12.2% vs. 19.3%). However, tocilizumab did not shorten hospital stay, reduce time to improved status, or improve mortality.

Vaccines

- **ASTRAZENECA's AZD-1222** – Although the clinical trial of this Covid-19 vaccine was allowed to resume in the U.K. and South Africa, in the U.S. the trial has been on hold since September 6 while the FDA and the data safety monitoring committee investigate the case of transverse myelitis that caused the halt. And there continues to be unconfirmed talk about a possible second case of transverse myelitis.
- **Attitudes** – Yet another survey found that a substantial number of Americans do not plan to get a Covid-19 vaccine as soon as it is available. A study of 1,000 consumers by Engine, a marketing company, found that 27% of respondents would get a Covid-19 vaccine as soon as one is available, but 77% would *eventually* get a vaccine. The AstraZeneca trial halt significantly reduced confidence in Covid-19 vaccines for 32% of respondents.
- **China** – The government approved a study of **Beijing Wantai Biological Pharmacy Enterprise**'s nasal spray Covid-19 vaccine, developed by Xiamen University and Hong Kong University researchers, that contains a weakened flu virus with genes from the SARS-CoV-2 spike protein.
- **Cost** – The Trump administration said there will be no out-of-pocket costs for Americans to get a Covid-19 vaccine, but, unless Congress changes the law, Medicare Part B may not cover vaccinations for Medicare beneficiaries because Medicare does not currently cover vaccines that do not have full FDA approval. That is, EUA vaccines are not covered.
- **Distribution** – CDC director Robert Redfield, MD, told a Senate hearing that states will need up to $6 billion to distribute a Covid-19 vaccine.
- **FDA EUA**
  - ✓ The FDA is ***considering*** tougher standards for a Covid-19 vaccine EUA. One expected change is a requirement that two-dose vaccines have at least 2 months of follow-up after trial participants have received their second dose. Another potential change is that the placebo group may be required to include at least 5 severe Covid-19 cases plus some positive cases in older

Covid-19 Vaccine Phase III Trial Protocols

Measurement	Moderna	AstraZeneca's AZD-1222	Pfizer and BioNTech	Johnson & Johnson	Novavax's NVX-CoV2373
Efficacy goal	60%	50%	60%	60%	N/A
Number of patients	30,000	30,000	29,481	60,000	10,000 in U.K. 30,000 in U.S.
Cases needed to prove efficacy	151	150	164	154	N/A
Shots (doses) required	2 (28 days apart)	1	2 (21 days apart)	1	2
Primary endpoint	Positive test + 2 symptoms	Positive test + 2 symptoms	Positive test + 1 symptom	Must include at least 5 cases of moderate-to-severe infection	Positive test or moderate/severe disease
Interim analysis	at 53 events and at 106 events	only at 75 cases	at 32, 62, 92 and 120 cases	77 cases	67% of cases
Timeline for knowing if the vaccine works	November	?? because trial on hold	late October	??	??

adults. It is not clear whether Health and Human Services Secretary Alex Azar will sign off on changes like that.

- ✓ New York Gov. Andrew Cuomo said New York will conduct its own review of any Covid-19 vaccine and would not trust an FDA approval.
- ✓ A panel was organized by the National Medical Association, which represents Black physicians, to vet any Covid-19 vaccine (or treatment) so the Black community can be reassured about their safety/efficacy.

- **Indemnification** – Europe reportedly plans to indemnify vaccine makers (at least partially) from lawsuits related to Covid-19 vaccines.
- **NOVAVAX's NVX-CoV2373** is the latest Covid-19 vaccine to enter Phase III. The U.K. trial will enroll 10,000 people, with at least 25% of patients age ≥65. It's a 2-dose regimen. A 30,000-patient trial is planned for the U.S. with a higher dose.
- **Pfizer** said the safety profile in its ongoing Phase III vaccine trial includes "mostly mild-to-moderate" side effects – mostly fatigue and headache, but also muscle pain, diarrhea, chills, and joint pain.
- **Russian vaccine Sputnik V** – Scientists who reviewed the clinical data that led to approval of this Covid-19 vaccine, published in ***The Lancet***, said they have concerns about "irregularities" in the data and are calling for the detailed data to be made public.
- **Trial protocols** – Moderna, AstraZeneca, Pfizer, and Johnson & Johnson all released the full protocol for their Phase III Covid-19 vaccine trials.

REGULATORY NEWS

Regulatory tidbits

- **Cannabis.** The FDA is encouraging the use of drug master files to support cannabis research.
- **Covid-19**
  - The FDA issued new guidance for drug companies on how to assess disease-related symptoms in clinical trials of drugs to prevent or treat Covid-19.
  - The FDA released comparative performance data for 55 authorized Covid-19 molecular diagnostic tests.
  - FDA Commissioner Stephen Hahn, MD, said the Agency will be issuing new guidance on what data is necessary to support an EUA of a Covid-19 vaccine.
- **FDA**
  - **Digital health** – The FDA launched its **Digital Health Center of Excellence** within the Center for Devices and Radiological Health (CDRH), which is dedicated to the advance of digital health technology, including mobile health devices.
  - **Drug imports** – The FDA issued final guidance for industry on importing drugs from Canada.
  - **Geriatrics** – The FDA issued draft guidance for industry on development of drugs and biologics for treating geriatric patients (age ≥65).
  - **Intended use** – The FDA proposed regulatory updates to clarify the types of evidence it will consider when determining the "intended use" of a product.
- **Kidney disease.** CMS approved a model – End-Stage Renal Disease ESRD Treatment Choices (ETC) — that encourages increased home dialysis use and kidney transplants. The new payment model goes into effect on January 1, 2021.
- **MFAR.** The Centers for Medicare and Medicaid Services (CMS) withdrew the proposed – and very controversial – Medicaid Fiscal Accountability Regulation (MFAR) designed to increase transparency in Medicaid financing.
- **Medicare Advantage programs.** Starting in 2022, CMS said it plans to rely exclusively on encounter data to calculate risk adjustment in Medicare Advantage and Part D plans.
- **Nursing homes**
  - CMS is providing an additional $165 million in supplemental funding to states for Money Follows the Person (MFP) demonstration programs aimed at moving individuals from nursing homes into community resources.
  - CMS changed its recommendations on nursing home visitors, saying family members should be allowed to visit if social distancing, masks, and hand-washing are observed, with outdoor visits preferable.
- **Opioids.** A federal appeals court struck down a lower court ruling that blocked the state of New York from collecting tax payments of ~$200 million from opioid makers and distributors to cover the costs of combating the opioid epidemic in that state.
- **Patient safety.** The Institute for Healthcare Improvement (IHI) and the Agency for Healthcare Research and Quality (AHRQ) jointly issued a national action plan for promoting patient safety.
- **Respiratory.** The FDA issued final guidance on development drugs to treat eosinophilic esophagitis. Notably, there is a change in how co-primary endpoint data should be analyzed.

- Sick leave. Changes by the U.S. Labor Department to the Families First Coronavirus Response Act clarify – and tighten – sick leave exemptions for healthcare providers.
- Spine surgery. CMS' proposed Medicare Physician Fee Schedule, if finalized, will cut payments for 26 spine surgeries by 5%-12% vs. 2020 rates.

FDA approvals

- 410 MEDICAL's LifeFlow, a rapid-infusion device, was granted expanded 510(k) clearance for use in delivering blood and blood components.
- ACUTUS MEDICAL's AcQMed, a 3D imaging and mapping catheter, was granted 510(k) clearance.
- ALAFAIR BIOSCIENCES' VersaWrap Nerve Protector, a hydrogel implant that protects and covers peripheral nerves, was granted 510(k) clearance.
- ALYDIA HEALTH's Jada, a device for treating and controlling abnormal postpartum uterine bleeding and postpartum hemorrhage, was granted 510(k) clearance.
- ASSURE TECH's Assure Covid-19 IgG/IgM Rapid Test Device was granted an EUA, making it the first authorized serology (antibody) test that can be used at point-of-care.
- AVINGER's Ocelaris Tigereye, an image-guided chronic total occlusion-crossing catheter system, was granted 510(k) clearance.
- BEARPAC MEDICAL's Passio, a pump drainage system for removing fluid from the lungs of patients with malignant and symptomatic pleural effusion, was granted 510(k) clearance.
- B-TEMIA's Keeogo Dermoskeleton, an exoskeleton human mobility system, was granted 510(k) clearance.
- CONTROLRAD's ControlRad Trace, was granted 510(k) clearance for use on OEC 9900 Mobile C-arms to reduce radiation during fluoroscopically-guided procedures.
- ENDO INTERNATIONAL/PAR STERILE PRODUCTS' dexmedetomidine hydrochloride, a generic sedative, was approved for use in intubated and mechanically ventilated patients. The FDA noted the increased demand for IV sedatives due to Covid-19.
- FITBIT's ECG App for assessing heart rhythm for atrial fibrillation was cleared for use.
- GLAXOSMITHKLINE's Nucala (mepolizumab) was approved to treat patients age ≥12 who have had hypereosinophilic syndrome (HES) for ≥6 months without another identifiable non-blood related cause of the disease.
- LIFE SPINE's Simpact, a sacroiliac joint fixation system, was granted expanded clearance for a 14.5 mm screw diameter.
- NOUS IMAGING's Framewise Integrated Real-Time MRI Monitoring software, which calculates patient motion during MRI head scans, was granted 510(k) clearance.
- ROCHE's CINtec Plus Cytology test was granted expanded approval for use as a triage for patients with a positive cobas HPV test.
- RTI SURGICAL's Dynamic Active Compression Plate, a fixation/stabilization plate for use on small bones in the foot, was granted 510(k) clearance.
- SPINEOLOGY's OptiMesh, an expandable interbody fusion system for use in lumbar fusion procedures, was granted de novo clearance.
- SURMODICS' Pounce Thrombus Retrieval System was granted 510(k) clearance for use in removing emboli and thrombi in patients with peripheral artery disease (PAD).
- VARIAN MEDICAL SYSTEMS' Eclipse v16.1, proton treatment planning software, was granted 510(k) clearance.
- VIDA DIAGNOSTICS' VIDA algorithm, an artificial intelligence-run software that analyzes lung scans, was granted 510(k) clearance.

FDA recalls/warnings

- ACELLA PHARMACEUTICALS' NP Thyroid is the latest hypothyroidism medication to be recalled (two lots) due to testing finding subpotent lots.
- Benadryl (diphenhydramine) – The FDA issued a warning to consumers, pharmacists, and healthcare professionals that taking higher than recommended doses of this over-the-counter allergy medicine can lead to serious heart problems, seizures, coma, or even death. The Agency noted that there have been reports of teenagers ending up in the emergency room or dying after participating in a "Benadryl Challenge."
- Benzodiazepines – The FDA added a boxed warning to ***all*** benzodiazepine medications warning about the risks of abuse, misuse, addiction, physical dependence, and withdrawal reactions.
- Covid-19 – Two website operators received a warning letter about marketing of unapproved Covid-19 products: **www.extrapharma.com** and **www.medication-house.com**.
- Dental amalgam – The FDA warn that people in the following groups may be at greater risk of an adverse event from mercury exposure due to dental amalgam: pregnant women (and their fetuses), women planning to become pregnant, nursing women and their newborns/infants, children age <6, people with pre-existing neurological disease or impaired kidney function.

- PERRIGO PHARMACEUTICAL's albuterol inhaler, manufactured by **Catalent Pharma Solutions**, was recalled due to possible clogging, which could cause patients not to receive enough (or any) drug.
- SUN PHARMACEUTICAL INDUSTRIES' Riomet ER (metformin extended-release) – One lot was recalled for unacceptable levels of NDMA.

European Regulatory News

- Covid-19
  - The European Medicines Agency (EMA) is requiring drug firms to publish clinical data after they get a marketing authorization for a Covid-19 vaccine or treatment.
  - **Dexamethasone** – The EMA endorsed use of this steroid to treat Covid-19 patients on oxygen or mechanical ventilation.
- ABBOTT's MitraClip G4, a transcatheter mitral valve repair (TMVR) system for treating mitral regurgitation, was granted a CE Mark.
- APOTEX's Upkanz (deferiprone) – The company withdrew its marketing application for this treatment for pantothenate kinase-associated neurodegeneration (PKAN) after it became clear the EMA would require additional efficacy data.
- ASTRAZENECA's Lynparza (olaparib) – The EMA's Committee for Medicinal Products for Human Use (CHMP) recommended expanded approval of this PARP inhibitor to include maintenance monotherapy treatment of ovarian cancer in specific patients.
- BRISTOL-MYERS SQUIBB
  - **Opdivo (nivolumab)** – CHMP recommended expanded approval of this PD-1 inhibitor to include first-line treatment of metastatic NSCLC without EGFR-mutation or ALK translocation.
  - **Yervoy (ipilimumab)** – CHMP recommended expanded approval of this CTLA4 inhibitor, in combination with Opdivo, to include first-line treatment for NSCLC patients without a EGFR-mutation or ALK translocation.
- CYTEK BIOSCIENCES' Cytek Northern Lights, a flow cytometer for clinical diagnostic use in laboratories, hospitals, and clinics, was granted a CE Mark.
- EISAI's Fycompa (perampanel) – CHMP recommended expanded approval to include treatment of partial-onset seizures in patients with or without secondarily generalized seizures in patients age ≥4 and to treat primary generalized tonic-clonic seizures in patients age ≥7 with idiopathic generalized epilepsy.
- EUROBIO SCIENTIFIC's EBX 042 FluCoSyn, a test that can identify and distinguish between influenza A and B, SARS-CoV-2, and respiratory syncytial virus (RSV), was granted a CE Mark.
- FIBRALIGN's BioBridge, a collagen matrix biodegradable mesh for use in treating lymphedema, was granted a CE Mark.
- FITBIT's ECG App for assessing heart rhythm for atrial fibrillation was granted a CE Mark.
- GENMARK DIAGNOSTICS' ePlex Respiratory Pathogen Panel 2, which can deliver results within two hours and can detect ~20 respiratory viruses and bacteria (e.g., influenza A and B, RSV, and SARS-CoV-2) was granted a CE Mark.
- GILEAD SCIENCES and GALAPAGOS' Jyseleca (filgotinib), an oral JAK1 inhibitor, was approved by the European Commission to treat active rheumatoid arthritis.
- GLAXOSMITHKLINE's Zejula (niraparib) – CHMP recommended expanded approval of this PARP inhibitor to include monotherapy maintenance in advanced epithelial high-grade ovarian, fallopian tube, or primary peritoneal cancer patients with a response (complete or partial) after first-line platinum-based chemotherapy.
- LILLY's Olumiant (baricitinib) – CHMP recommended expanded approval of this JAK inhibitor to include treatment of moderate-to-severe atopic dermatitis.
- MEDOVATE's Safira, an anesthesia device which allows a single doctor to handle anesthesiology procedures, was granted a CE Mark.
- OTSUKA's Deltyba (delamanid) – CHMP recommended expanded approval of this antibiotic to treat multi-drug resistant tuberculosis in adolescents and children.
- PACIRA BIOSCIENCES' Exparel (bupivacaine) – CHMP recommended approval to treat post-operative pain.
- PFIZER
  - **Nyvepria (pegfilgrastim)** – a biosimilar of Amgen's Neulasta – CHMP recommended approval of this leukocyte growth factor to reduce the duration of neutropenia and the incidence of febrile neutropenia after cytotoxic chemotherapy.
  - **Zavicefta (ceftazidime + avibactam)** – CHMP recommended expanded approval of this antibiotic to include treatment of complicated intra-abdominal infections, complicated urinary tract infections, and hospital-acquired pneumonia.

- ROCHE'S Tecentriq (atezolizumab) – CHMP recommended expanded approval of this PD-L1 inhibitor, in combination with Avastin (bevacizumab), as first-line treatment for hepatocellular carcinoma (HCC).
- SANOFI
  - MenQuadfi – CHMP recommended approval of this meningococcal vaccine.
  - Supemtek – CHMP recommended approval of this quadrivalent influenza vaccine.
- SEQIRUS' Flucelvax Tetra – CHMP recommended expanded approval of this influenza vaccine to treat children as young as 2.
- SFL REGULATORY SERVICES' obiltoxaximab SFL – CHMP recommended approval to treat or as post exposure prophylaxis of inhalation anthrax.
- STEMLINE THERAPEUTICS' Elzonris (tagraxofusp) – At the company's request, CHMP started a re-examination of this CD123-directed cytotoxin for treating blastic plasmacytoid dendritic cell neoplasms.
- VERTEX PHARMACEUTICALS
  - Kalydeco (ivacaftor) – CHMP recommended expanded approval to include a new 75 mg strength and to allow use in children with cystic fibrosis as young as 6.
  - Symkevi (tezacaftor + ivacaftor) – CHMP recommended expanded approval to include a new dosage (50/75 mg) and to allow use in children as young as 6.
- VIFOR FRESENIUS MEDICAL CARE'S Velphoro (sucroferric oxyhydroxide) – CHMP recommended approval to treat children as young as 2 with chronic kidney disease on dialysis.

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

- AKCEA THERAPEUTICS' Waylivra (volanesorsen) – NICE reversed its earlier decision after the company discounted the price and now is recommending use of this apoC3 inhibitor to treat familial chylomicronemia syndrome.
- ASTRAZENECA'S Tagrisso (osimertinib) – NICE recommended use of this third-generation EGFR inhibitor to treat treatment-naïve adults with locally-advanced/metastatic EGFR-mutation-positive NSCLC.

Regulatory news from other countries

- *China.* MINORYX THERAPEUTICS' leriglitazone – The rights in China to this PPAR-γ agonist for treating X-linked adrenoleukodystrophy (X-ALD) were exclusively licensed to **Sperogenix Therapeutics**.
- *Japan.*
  - GALAPAGOS and GILEAD SCIENCES' Jyseleca (filgotinib), an oral JAK1 inhibitor, was approved by the Ministry of Health, Labour, and Welfare (MHLW) as a treatment for rheumatoid arthritis.
  - ROCHE and CHUGAI's Tecentriq (atezolizumab) – The MHLW granted expanded approval for this PD-L1 inhibitor, in combination with Avastin (bevacizumab), as a first-line treatment for hepatocellular carcinoma (HCC).
- *Taiwan.* B-TEMIA's Keeogo Dermoskeleton, an exoskeleton human mobility system, was cleared for use by Taiwan's Food and Drug Administration.

2020 FDA Advisory Committees and Other Regulatory Dates of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
September 29	**Patient preference information use** in medical device regulatory decisions	FDA public meeting webcast
September 29 *and* Oct. 1	FDA regulation of **reproductive tissues**	FDA virtual public workshop
September 30	Global summit on regulatory science: **Emerging Technologies**	FDA's National Center for Toxicological Research virtual summit
September 30	**Patient-reported outcomes** (PROs) and medical device evaluations	FDA virtual public meeting
September 30	**Mesoblast's Kyoncil** (remestemcel-L) for steroid-refractory acute graft-versus-host disease in pediatric patients	PDUFA date
October 2	Discussion of strains to be included in **flu virus vaccine** for 2021 southern hemisphere flu season	FDA's Vaccines and Related Biological Products Advisory Committee virtual meeting
October 2	Control of **nitrosamine** impurities in human drugs	FDA webinar
October 6	Patient-focused drug development for **stimulant use disorder**	FDA virtual public meeting
October 7	**TransMedics' TransMedics Organ Care System** (OCS) – normothermic heart transplant transport	FDA's Circulatory System Devices Advisory Committee virtual meeting
October 8	Assessing changes in the PK of drugs in **liver disease**	FDA virtual public workshop in collaboration with the University of Maryland Center of Excellence in Regulatory Science & Innovation
October 8	**Arbor Pharmaceuticals' amphetamine sulfate immediate-release** for treating attention-deficit/hyperactivity disorder (ADHD)	FDA's Psychopharmacologic Drugs Advisory Committee joint *virtual* meeting with the Drug Safety and Risk Management Advisory Committee
October 8	Bioequivalence of complex **topical generic drugs** (*in vitro* and *in vivo*)	FDA webcast
October 9	**Alkermes' ALKS-3831** (olanzapine/samidorphan) for schizophrenia and bipolar disorder	FDA's Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee joint virtual meeting
October 9	**NanoDay Virtual Research Symposium**	FDA Nanotechnology Task Force virtual meeting
October 13	Patient-focused drug development for **systemic sclerosis**	FDA virtual public meeting
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 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	Complex generic **drug-device combination products**	FDA/DIA virtual conference
October 19	Digital Health Center of Excellence **Listening Session #1**	FDA webcast
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 22-23	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

more - 2020 FDA Advisory Committees and Other Regulatory Dates of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
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 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 20	**Eiger BioPharmaceuticals' Zokinvy** (lonafarnib) for progeria and progeroid laminopathies	PDUFA date
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 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