TRENDS-in-MEDICINE

May 23, 2021

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…

Trends-in-Medicine
Stephen Snyder, *Publisher*
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-285-0801
Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

NOTE: Subscribe to ***Trends-in-Medicine*** for detailed coverage of the FDA and CDC approval of **Pfizer and BioNTech's Covid-19 vaccine** for adolescents, the virtual **American Society for Gene and Cell Therapy** (ASGCT) meeting, the virtual **American College of Cardiology** (ACC) meeting, and the virtual **Digestive Disease Week** (DDW) meeting. Our Covid-19 Update starts on page 5.

Top news of the week

✓ **Atopic dermatitis** – An ICER review of 5 drugs showed pluses and minuses for each, with **Pfizer's abrocitinib**, an oral JAK inhibitor, the most effective but overpriced by 44%-77%.

✓ **Positive trial news:**

- **ACCELERON PHARMA's sotatercept** – in pulmonary arterial hypertension (PAH).
- **ANNOVIS BIO's Posiphen (ANVS-401)** – in Parkinson's disease.
- **ASTRAZENECA**
  - **and DAIICHI SANKYO's datopotamab deruxtecan** – in triple-negative breast cancer (TNBC).
  - **and AMGEN's tezepelumab** – in asthma.
- **BAYER's finerenone** – in patients with CKD and Type 2 diabetes.
- **BOSTON SCIENTIFIC's**
  - **ACURATE neo2** – in aortic stenosis.
  - **Watchman FLX** – for atrial fibrillation.
- **INCYTE's ruxolitinib** (topical) – in vitiligo.
- **LILLY's tirzepatide** – in cardiovascular outcomes in Type 2 diabetes.
- **MEDTRONIC's Evolut** – at 2 years in low-risk TAVR patients.
- **MERCK MSD's**
  - **Keytruda** (pembrolizumab) – in triple-negative breast cancer.
  - **V114** – in pneumonia.
- **ORCHARD THERAPEUTICS' OTL-101** – in adenosine deaminase severe combined immunodeficiency (ADA-SCID).
- **REGENERON PHARMACEUTICALS and SANOFI's**
  - **Libtayo** (cemiplimab) – in advanced cervical cancer.
  - **Dupixent** (dupilumab) – in moderate-to-severe asthma.

- **ROCHE's**
  - – **Avastin** (bevacizumab) – in diabetic macular edema.
  - – **Rituxan** (rituximab) – in pemphigus vulgaris.

✓ **Negative trial news:**

- **BIOGEN's cotoretigene toliparvovec** – in X-linked retinitis pigmentosa.
- **IDERA PHARMACEUTICALS' tilsotolimod** – in refractory advanced melanoma.

SHORT TAKES

- **ABBVIE/ALLERGAN AESTHETICS** is buying **Soliton**, which will give it RESONIC, a rapid acoustic pulse device for non-invasive treatment of cellulite and for tattoo removal.

- **ACCELERON PHARMA's sotatercept** – Interim results from the open-label extension of the Phase II PULSAR trial in pulmonary arterial hypertension (PAH), presented at the American Thoracic Society (ATS) virtual conference, showed that this fusion protein maintained or improved responses on multiple efficacy endpoints for up to 48 weeks. In addition, placebo patients switched to sotatercept improved.

- **AGENUS' AGEN-1777**, an anti-TIGIT, plus another undisclosed agent were licensed exclusively to **Bristol-Myers Squibb**, which will become responsible for development and commercialization worldwide.

- **ANNOVIS BIO's Posiphen (ANVS-401)** – In a small, short Phase II trial of 14 Parkinson's disease patients and 14 Alzheimer's disease patients, this enantiomer of phenserine significantly improved ADAS-Cog11 scores (by ~30% vs. baseline, p=0.04) at Day 25. The Parkinson's patients also showed significant reduction in several inflammatory disease markers.

- **AVENDA HEALTH**'s prostate cancer lumpectomy technology was granted breakthrough device status by the FDA.

- **BEIGENE's Brukinsa (zanubrutinib)** – The supplemental new drug application (sNDA) for this BTK inhibitor was granted priority review by the FDA as a treatment for marginal zone lymphoma.

- **BLUEBIRD BIO** was sued by **Roche/Spark Therapeutics** for using the word "spark" in its gene therapy advertising.

- **BRISTOL-MYERS SQUIBB** expanded its collaboration with **Exscientia**, focused on small molecules in oncology and immunology, with Exscientia taking responsibility for artificial intelligence design and discovery.

- **CHARLES RIVER LABORATORIES** is buying **Vigene Biosciences**, a gene therapy contract development and manufacturing organization (CDMO).

- **COMPASS THERAPEUTICS** is buying **TRIGR Therapeutics**, which will give it TR-009 (renamed CTX-009), a bispecific targeting DLL4/VEGF-A for solid tumors.

- **CYTODYN's leronlimab** – In a rare move, the FDA made it clear that the data on this CCR5 antagonist show it does ***not*** work in Covid-19. The FDA basically slammed the company for trying to put a positive spin on the data, emphasizing that leronlimab missed the primary and secondary endpoints in the pivotal trial, and slicing and dicing to find a positive subgroup analysis is, at best, unreliable. The FDA's bottom line: *"The data currently available from recent CytoDyn clinical trials do not support the clinical benefit of leronlimab for the treatment of Covid-19."*

- **DAVITA KIDNEY CARE** is expanding its home kidney care program with the inclusion of **Baxter**'s HomeChoice Claria Automated Peritoneal Dialysis (APD) system with remote patient monitoring.

- **DERMASENSOR's DermaSensor**, a skin cancer detection device, was granted breakthrough device status by the FDA.

- **EMMES**, a global contract research organization (CRO), bought a U.K. CRO – **Orphan Reach**.

- **EXELIXIS' Cabometyx (cabozantinib)** – **Ipsen** is collaborating with Exelixis on the pivotal Phase III COSMIC-311 trial of this targeted therapy in radioiodine-refractory differentiated thyroid cancer (DTC) patients who progressed after ≤2 prior VEGFR-targeted therapies.

- **GINKGO BIOWORKS** is buying **Dutch DNA Biotech**, which has proprietary platform technology focused on development of fungal strains and fermentation processes for production of proteins and organic acids.

- **GLAXOSMITHKLINE** plans to sell its stake in **Innoviva**, a royalty management company that collaborates with GSK on respiratory treatments.

- **HELIO HEALTH** is partnering with **Fujifilm Medical Systems** on development of a blood-based test for detecting liver cancer early.

- **IDERA PHARMACEUTICALS' tilsotolimod** – The company is giving up on the Phase III trial of this intratumoral TLR9 agonist in refractory advanced melanoma. It missed the primary endpoint, and Idera is not waiting for overall survival data.

- **INCYTE's ruxolitinib** – This topical JAK inhibitor formulation met the primary endpoint in the pivotal Phase III TRuE-V trial in vitiligo, with significantly more patients having a ≥75% improvement in facial vitiligo vs. placebo at Week 24.

- **IONIS PHARMACEUTICALS** ended its inhaled IONIS-ENAC-2.5-Rx program in cystic fibrosis after a long-term animal toxicology study raised safety issues.

- **IOVANCE BIOTHERAPEUTICS' lifileucel (LN-145)** – The FDA is requiring additional potency assay data on this tumor-infiltrating lymphocyte (TIL) therapy for metastatic melanoma, which is likely to delay a biologics license application (BLA) filing until 1H22. After making this announcement Iovance's CEO quit.

- **MDIMUNE** is collaborating with **Reyon Pharmaceuticals**, which will use its cell-derived vesicle platform in the delivery of an mRNA vaccine against an undisclosed virus and in an mRNA treatment for an undisclosed rare genetic disorder.

- **MEDTRONIC's Evolut** – Two-year outcomes data in low-risk patients, presented at the virtual EuroPCR meeting, showed that this transcatheter aortic valve replacement (TAVR) was non-inferior to open-heart surgery in terms of safety, with a death or disabling stroke rate of 4.3% vs. 6.3% for surgery.

- **NOVARTIS** is partnering with **Ada Health** to use Ada's artificial intelligence diagnosis platform for tracking rare conditions and immunological diseases.

- **NOVOCURE's Tumor Treating Fields (TTF)** – The FDA approved an investigational device exemption (IDE) supplement for the Phase III LUNAR trial in non-small cell lung cancer (NSCLC), allowing the company to reduce enrollment from 534 to 276 and the follow-up period from 18 to 12 months, given the positive interim analysis announced last month.

- **OMEROS' narsoplimab** – The FDA extended its review of the BLA for this treatment for hematopoietic stem cell transplant-associated thrombotic microangiopathy. The new PDUFA date is October 17, 2021.

- **ORCHARD THERAPEUTICS' OTL-101** – In three Phase I/II trials with a total of 50 patients, this gene therapy for adenosine deaminase severe combined immunodeficiency (ADA-SCID) showed 100% overall survival and ~95% event-free survival at 2 and 3 years with a single treatment.

- **PERKINELMER** is buying **Immunodiagnostic Systems**.

- **PFIZER** plans to use **Iktos** for de novo design of "selected Pfizer small-molecule discovery programs."

- **SANOFI/GENZYME's Lemtrada (alemtuzumab)**, an anti-CD52, will be used, through a collaboration with **Cellectis**, as a lymphodepleting regimen in some Cellectis-sponsored UCART trials.

- **SIGA TECHNOLOGIES' TPOXX IV (intravenous tecovirimat, ST-246)** – A new drug application (NDA) for an intravenous formulation of this smallpox treatment was submitted to the FDA. *Remember, the oral formulation is already FDA approved.*

- **SURGALIGN SPINE TECHNOLOGIES**' digital surgical guidance system, which provides intuitive visualization of the patient's internal anatomy and real-time surgical guidance based on intraoperative 3D scans, was submitted to the FDA through the 510(k) pathway.

- **TAKEDA's maribavir** – The FDA accepted an NDA for review for this antiviral and granted it priority review to treat cytomegalovirus (CMV) infection in solid organ or hematopoietic cell transplant recipients. The PDUFA date is in November 2021.

- **TELEFLEX** is selling its Hudson RCI brand of respiratory products to **Medline**.

NEWS IN BRIEF

ASTRAZENECA

- **and DAIICHI SANKYO's datopotamab deruxtecan.** Updated data on this antibody-drug conjugate from the Phase I TROPION-PanTumor01 trial in triple-negative breast cancer (TNBC), presented at the virtual ESMO Breast meeting, showed a 43% response rate, with 5 confirmed complete or partial responses (and 4 unconfirmed CR/PRs) out of 21 patients, most of whom were treated at the 6 mg dose.

- **and AMGEN's tezepelumab.** New data from the Phase III NAVIGATOR trial of this first-in-class TSLP inhibitor in asthma, published in the ***New England Journal of Medicine***, showed that adding tezepelumab to standard of care was superior on the primary and all key secondary endpoints vs. standard of care alone. Among the new pre-specified exploratory analyses were subgroup analyses of reduction in annualized exacerbation rates over 52 weeks.

Atopic dermatitis – an ICER analysis

The Institute for Clinical and Economic Review (ICER) released a draft report on five new/investigational treatments for atopic dermatitis (AD) – comparing them to Regeneron Pharmaceuticals and Sanofi's Dupixent (dupilumab), an anti-IL-4.

- **AbbVie's Rinvoq (upadacitinib)**, an oral JAK inhibitor for moderate-to-severe AD.

- **Incyte's ruxolitinib**, a topical JAK inhibitor for mild-to-moderate AD.
- **Leo Pharma's Adtralza (tralokinumab)**, a subcutaneous anti-IL-13 – "some concerns about safety."
- **Lilly and Incyte's Olumiant (baricitinib)**, an oral JAK inhibitor for moderate-to-severe AD – not enough evidence for evaluation.
- **Pfizer's abrocitinib (PF-04965842)**, an oral JAK inhibitor for moderate-to-severe AD – does not appear to add any effectiveness.

ICER found:

- **Upadacitinib, tralokinumab, baricitinib, and abrocitinib** all improved itch, sleep, and quality of life vs. placebo. The efficacy evidence "is promising but inconclusive."
- The net health benefit of the **3 oral JAK inhibitors** vs. topical therapies was "promising" (but inconclusive), and the data were insufficient to compare them to each other.
- The net health benefit of **abrocitinib** and **upadacitinib** vs. dupilumab was "insufficient."
- **Baricitinib** and **tralokinumab** were "comparable or inferior" to dupilumab.
- **Abrocitinib** had the highest efficacy, but it was ***not*** the most cost-effective. Its $64,300 list price would need to be reduced by 44%-77% to be cost-effective.
- **Ruxolitinib** was more effective than placebo and maybe more effective than potent topical corticosteroids, but long-term safety is unknown. Efficacy is comparable or better than topical emollients, but evidence vs. other topical medications was insufficient. However, efficacy may be lower in people with dark skin.

Cost-Effectiveness of New AD Therapies

Company	Drug	Comparator	Cost per QALY gained	Annual Price to be Cost-Effective
Pfizer	abrocitinib	Standard of care	$ 167,000	$ 37,500
Lilly and Incyte	baricitinib	Standard of care	$ 86,000	$ 31,300
Leo Pharma	tralokinumab	Standard of care	$ 147,000	$ 31,700
AbbVie	upadacitinib	Standard of care	$ 275,000	$ 36,200
Regeneron	dupilumab	Standard of care	$ 132,000	$ 34,900
Pfizer	abrocitinib	dupilumab	$ 308,000	--
Lilly and Incyte	baricitinib	dupilumab	Less costly, less effective	--
Leo Pharma	tralokinumab	dupilumab	Less costly, less effective	--
AbbVie	upadacitinib	dupilumab	Less costly, more effective	--

BAYER's finerenone

This anti-mineralocorticoid:

- Met the primary endpoint in a second Phase III study, the ~7,400-patient FIGARO-DKD cardiovascular outcomes trial in patients with chronic kidney disease (CKD) and Type 2 diabetes, significantly reducing the risk of time to first occurrence of cardiovascular death or non-fatal cardiovascular events.
- Significantly reduced the risk of new-onset atrial fibrillation or atrial flutter in a pre-specified exploratory analysis of the FIDELIO-DKD trial – published in the ***Journal of the American College of Cardiology*** – in patients with CKD and Type 2 diabetes (3.2% vs. 4.5% with placebo, a 29% relative risk reduction).

BIOGEN

- **Cotoretigene toliparvovec.** This gene therapy for X-linked retinitis pigmentosa (XLRP) missed the primary endpoint in the 41-patient Phase II/III XIRIUS trial, failing to improve retinal sensitivity at 12 months on a macular integrity test, though there were some positive trends on secondary endpoints.
- Exercised its option to buy **TMS' TMS-007**, a next-generation thrombolytic for acute ischemic stroke, after examining the results of a 90-patient Phase IIa trial. No patients in the TMS-007 arm had symptomatic intracranial hemorrhage (sICH), a side effect that deters physicians from using other drugs.

BOEHRINGER INGELHEIM

New data were presented at the virtual ATS meeting from three analyses reinforcing the importance of adhering to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations when prescribing treatments for chronic obstructive pulmonary disease (COPD) patients – that escalate to triple therapy (long-acting muscarinic antagonist + long-acting β_2-agonist + inhaled corticosteroids, LAMA/LABA + ICS) for initial maintenance treatment of COPD.

- An analysis that showed initiating LAMA therapy decreased the escalation rate to triple therapy vs. initiation of LABA/ICS therapy.
- An analysis that showed no differences in all-cause mortality between LAMA/LABA and triple therapy.
- An analysis showing wide geographic disparity in how GOLD recommendations are followed.

BOSTON SCIENTIFIC

Data presented at the virtual EuroPCR meeting included:

- **ACURATE neo2**
  - In the EARLY neo2 registry, this transcatheter aortic valve showed a low rate (1.3% moderate-severe, 33.3% mild, and 65.4% none/trace) of paravalvular leakage (PVL) and a low (6%) permanent pacemaker implantation.
  - In the ITAL-neo registry, ACURATE neo showed a 3.1% rate of moderate/severe PVL, with 40% none/trace.
- **Watchman FLX.** The European Alster-FLX Registry showed that this left atrial appendage closure device had a high device closure rate and good clinical safety and efficacy (device closure rate) outcomes.

LILLY

- Is collaborating with **MiNA Therapeutics**, using MiNA's saRNA technology platform to develop up to five novel drug candidates across various diseases.
- **and INNOVENT's sintilimab** (Tyvyt in China), an anti-PD-1, was submitted to the FDA for use in combination with pemetrexed (Lilly's Alimta) + platinum chemotherapy as a first-line treatment for non-squamous NSCLC. The PDUFA date is in March 2022.
- **Tirzepatide**, a dual GIP/GLP-1 receptor agonist, met the primary and key secondary endpoints in yet another Phase III trial vs. Sanofi's Lantus (insulin glargine) in Type 2 diabetes patients at increased cardiovascular risk. HbA_{1c} was significantly lower with all tirzepatide doses at Week 52, and patients lost weight with tirzepatide vs. a gain with Lantus.

MERCK MSD

- **Keytruda (pembrolizumab).** In an interim analysis this PD-1 inhibitor, added to chemotherapy, met both primary endpoints in the pivotal Phase III KEYNOTE-522 trial in triple-negative breast cancer (TNBC), with significantly better event-free survival and pathological complete response (pCR) vs. chemotherapy alone.
- **V114.** In top-line results from the Phase III PNEU-DIRECTION and PNEU-PLAN pediatric trials, this 15-valent pneumococcal conjugate vaccine met the primary immunogenicity and safety endpoints.

REGENERON PHARMACEUTICALS and SANOFI

- **Libtayo (cemiplimab-rwlc).** In Phase III data presented at the European Society for Medical Oncology (ESMO) Breast Cancer virtual meeting, this PD-1 inhibitor improved overall survival, progression-free survival (PFS), and objective response rate (ORR) vs. chemotherapy in second-line recurrent/metastatic cervical cancer patients who had previously progressed on chemotherapy.
- **Dupixent (dupilumab).** Pediatric data from a Phase III trial, presented at the ATS virtual meeting, showed that this anti-IL-4, improved lung function in children age 6-11 with moderate-to-severe asthma and type 2 inflammation. Dupixent also significantly improved overall asthma symptom control and reduced fractional exhaled nitric oxide (FeNO).

ROCHE

- **Avastin (bevacizumab).** A study, published in ***Therapeutic Advances in Ophthalmology***, found that diabetic macular edema (DME) patients treated with intravitreal Avastin plus grid laser photocoagulation was more effective in managing diffuse DME vs. laser alone.
- **Rituxan (rituximab).** In a study, published in the ***New England Journal of Medicine***, this anti-CD20 showed superiority to mycophenolate mofetil (Roche's CellCept) in achieving and maintaining a complete remission at Week 52 in patients with moderate-to-severe pemphigus vulgaris.

COVID-19 UPDATE

- **Numbers**
  - **Globally**, there have been 166,436,448 cases and 3,449,371 deaths, a mortality rate of 4.5 per 100,000 people or ~1 in every 25,000 people.
  - In the **U.S.**, there have been 33,102,724 confirmed cases of Covid-19 (which means 10% of the population contracted the virus at some point in the past ~15 months. There have also been 589,664 deaths (17% of the worldwide Covid-19 death total – a share which has been slowly but steadily declining since vaccinations started). The mortality rate is 180 per 100,000 people or nearly 2 per 1,000 people in the country.
  - **Vaccinations.** As of May 22, 162 million people in the U.S. (49% of the population) had received at least one dose of a Covid-19 vaccine, and 129 million (39%) were fully vaccinated. Worldwide, 383 million people have been fully vaccinated (5% of the world population).
  - **India** has the second highest count of Covid-19 cases (26,530,132), with 299,266 deaths, a per capital mortality rate of 22 per 100,000 people, but case and perhaps fatality under-counting are very likely.

Masks

- The Centers for Disease Control and Prevention (CDC) said that people who are fully vaccinated can resume normal activities without wearing a mask or social distancing, unless required by governmental regulations (planes, trains, etc.) or individual businesses. Some chains (e.g., Walmart and Publix) eliminated their mask mandate, but others (e.g., Target) did not.
- **Schools.** A Georgia study of 169 K-5 schools found that Covid-19 infection rates were 37% lower in schools where teachers and staff members were required to wear masks. However, there was no significant difference between schools that did and did not require students to wear a mask.

Non-Covid vaccines.

The CDC's Advisory Committee on Immunization Practices said that there no longer has to be a two-week waiting period after the last Covid-19 vaccine dose and administration of other vaccines.

Testing.

The FDA advised against use of SARS-CoV-2 antibody tests to evaluate protection from a Covid-19 vaccine.

Travel.

It is increasingly likely that vaccinated Americans (and people from countries with low Covid-19 rates) will be able to travel to Europe this summer, but exactly when is still not clear, and the conditions may vary from country to country. *Check carefully before you buy tickets.*

Treatment

- **ASTRAZENECA's AZD-7442** – The U.K. government is reportedly rethinking its in-principle agreement to buy one million doses of this long-acting antibody.
- **CYTODYN's leronlimab** – In a rare move, the FDA made it clear that the data on this CCR5 antagonist show it does ***not*** work in Covid-19.
- **REGENERON PHARMACEUTICALS' REGEN-COV (casirivimab + imdevimab)** – A study of this two-drug antibody cocktail showed an ~70% reduction in the risk of hospitalization or death in outpatients with Covid-19.

Vaccines

- **Booster shots** are looking more and more likely, but timing is still uncertain.
  - Peter Marks, MD, PhD, Director of the FDA's Center for Biologics Evaluation and Research (CBER) said, "It would be nice if it'll turn out that it'll be a year before anyone might need a booster…but we still don't know. It could be more; it could be less."
  - Pfizer CEO Albert Bourla, DVM, PhD, said people will "likely" need a booster every 12 months – similar to an annual flu shot.
  - However, not all experts agree with that. Former CDC Director Thomas Frieden, MD, said, "There is zero, and I mean zero, evidence to suggest that that is the case… It's completely inappropriate to say that we're likely to need an annual booster because we have no idea what the likelihood of that is."
  - And a World Health Organization official expressed concern that a focus on vaccinating adolescents or giving vaccinated people booster shots will slow vaccinations in poorer nations.
- **Cardiac problems** – The CDC's Covid-19 Vaccine Safety Technical Work Group is investigating what it said is a small number of young adults and adolescents who experienced heart problems (myocarditis) after an mRNA vaccine, most often after the second dose, but it is not yet clear that the vaccine is responsible. The American Heart Association issued a statement that the benefits of the vaccines "enormously outweigh the rare, possible risk of heart-related complications."
- **Herd immunity** – In eight states at least 70% of adults have been vaccinated – Connecticut, Hawaii, Maine, Massachusetts, New Hampshire, New Jersey, Rhode Island, and Vermont.
- **Infections in vaccinated people** – Eight New York Yankee baseball players tested positive for Covid-19 more than two weeks after their last Covid-19 vaccination. All but one were asymptomatic.
- **Mix-and-match vaccines.** A study found that mixing Covid-19 vaccines could lead to more frequent side effects.
- **Olympics** – So far, the Summer Olympics in Tokyo, Japan, are still on. Japanese regulators issued an emergency use authorization for both the AstraZeneca and Moderna vaccines.
- **ASTRAZENECA's Vaxzevria (AZD-1222)**
  - The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) is reviewing reports of Guillain-Barré in people given this vaccine.
  - **Indonesia** halted use of the 448,480 vaccine doses it received after a 22-year-old man died a day after getting the vaccine.
- **JOHNSON & JOHNSON's Ad26.COV2.S** – Germany has authorized use for all adults in that country.

- **MEDICAGO and GLAXOSMITHKLINE's COVLP** – Interim results from a Phase II trial showed neutralizing antibody responses were high after two doses of this plant-derived adjuvanted vaccine in people age 18-64 and in the elderly (age ≥65).
- **PFIZER and BIONTECH's BNT-162b2**
  - A British study found that delaying administration of the second dose to 12 weeks after the first dose instead of 3 weeks resulted in a 3.5-fold increase in SARS-CoV-2 antibodies.
  - An Israeli study , published in ***Therapeutic Advances in Neurological Disorders***, found that for multiple sclerosis patients, the type of disease-modifying therapy (DMT) they are on affects the development of protective antibodies after getting this vaccine. Immunity developed in 100% of patients on no DMT or on cladribine (Merck KGaA's Mavenclad), but only 22.7% of patients on ocrelizumab (Roche's Ocrevus) and 3.8% of patients on Novartis' Gilenya (fingolimod).
  - The FDA authorized a longer refrigerator storage time (1 month) for thawed BNT-162b2 vaccine doses.
- **SINOPHARM's vaccine** was approved by WHO, making it the first Chinese-made vaccine to get emergency use authorization from WHO. Residents of the United Arab Emirates (UAE) who received two doses of this vaccine six months ago are being offered a third dose to boost efficacy.

Variants. Two separate studies showed good activity of mRNA vaccines against variants:

- A preprint study on ***boRxiv*** found that both the Pfizer and Moderna vaccines are effective against the U.K. (B.1.1.7) and South Africa (B.1.351) variants.
- Another study found that a third dose of the AstraZeneca vaccine offered protection against "almost any variant."

REGULATORY NEWS

Regulatory tidbits

CMS

- The Centers for Medicare and Medicaid Services (CMS) will now require nursing homes to report Covid-19 vaccination rates.
- CMS postponed the compliance date for the Medicare Coverage of Innovative Technology final rule from May 15 to December 15, 2021.

EPA. The Inspector General of the Environmental Protection Agency urged EPA to conduct another review of the residual cancer risk from ethylene oxide emission from medical device sterilization facilities.

FDA

- **340B.** The Health Resources and Services Administration (HRSA) notified six drug companies – AstraZeneca, Lilly, Novartis, Novo Nordisk, Sanofi, and United Therapeutics – that they are violating federal law by restricting safety net provider access to products discounted under the 340B program.
- **Biowaivers.** The FDA issued guidance on classification of drug substances that is intended to reduce the need for *in vivo* studies to establish bioequivalence.
- **Covariates.** The FDA issued draft guidance on use of covariates in clinical trials.
- **Diabetes.** The FDA issued draft guidance on early clinical studies for certain medical devices (e.g., neurostimulators) intended to improve glycemic control for Type 2 diabetes.
- **Generic drugs.** The FDA issued a batch of product-specific guidances for developing generic drugs.
- **Infectious diseases.** The FDA issued final guidance for its qualified infectious disease product designation program, and it includes clarification on what is considered an antibacterial or antifungal drug.
- **Inspections.** The FDA set a "roadmap" for getting back on track with plant inspections. However, the Agency said it will conduct less than half of planned inspections in FY21 because of the pandemic and is unsure when it will be able to resume normal domestic inspections.
- **Manufacturing.** The FDA issued final guidance on post-approval changes in a drug's manufacturing.
- **Paralysis.** The FDA issued final guidance on brain-computer interface technology.
- **Peptides.** The FDA is asking for comments on the pharmacological evaluation of peptides.
- **Pooled data.** The FDA's Oncology Center of Excellence is using crowdsourcing to get input on ideas for use of pooled data in oncology trials.
- **Product lifecycle.** The FDA issued final guidance on pharmaceutical product lifecycle management (ICH Q12).
- **Sunscreens.** The FDA said it is preparing an environmental impact statement on sunscreen products.

Fentanyl. The Biden administration extended the ban on addictive fentanyl-like substances (fentanyl analogs), which are Schedule I drugs, to October 2021.

- **Telehealth.** The Government Accountability Office (GAO) urged Congress to wait until the end of the pandemic before making a decision about a permanent expansion of telehealth in Medicare and Medicaid.
- **WHO.** The World Health Organization and the International Coalition of Medicines Regulatory Authorities (ICMRA) called on the drug industry to offer voluntary, unrestricted access to clinical trial data for new medicines and vaccines without redaction of confidential information.

FDA approvals/clearances

- **APELLIS PHARMACEUTICALS and SOBI's Empaveli (pegcetacoplan)**, a C3 inhibitor, was approved to treat paroxysmal nocturnal hemoglobinuria (PNH).
- **BIGFOOT BIOMEDICAL's Bigfoot Unity**, a smart cap for insulin pens, was granted 510(k) clearance for use by diabetics needing multiple insulin injections per day.
- **BIOREZ's BioBrace Implant**, a soft-tissue scaffold for use in various surgical procedures, was granted 510(k) clearance.
- **BRISTOL-MYERS SQUIBB's Opdivo (nivolumab)** was approved for the adjuvant treatment of completely resected esophageal or gastroesophageal junction (GEJ) cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy (CRT). This is the first immunotherapy approved in this patient population.
- **CONFORMIS' Identity Imprint**, a total knee replacement system, was granted 510(k) clearance.
- **GE HEALTHCARE's AIR Recon DL**, a machine learning-based image reconstruction system for use with its SIGNA 7.0 tesla MRI scanner, was granted 510(k) clearance.
- **GUARDANT HEALTH's GUARDANT360 CDx** was approved as a companion diagnostic for Johnson & Johnson/Janssen's Rybrevant in NSCLC.
- **HERON THERAPEUTICS' Zynrelef (bupivacaine + meloxicam, HTX-011)**, an extended-release dual-acting local anesthetic, was approved for the management of postoperative pain for up to 72 hours.
- **ICE NEUROSYSTEMS' iCE-SG Subcutaneous Electrode**, a brain monitor for critically ill patients wh-o have or are at risk of brain injury, was granted 510(k) clearance.
- **JOHNSON & JOHNSON**
  - **Acuvue Abiliti**, an overnight contact lens for management of myopia in children, was cleared for use.
  - **Rybrevant (amivantamab-vmjw)** was approved as the first treatment for adults with NSCLC with an EGFR exon 20 insertion mutation.
  - **Tecnis Synergy and Tecnis Synergy Toric II**, implantable intraocular lenses, were cleared for use.
- **MEDO's Medo-Thyroid software**, an artificial intelligence-powered tool to help with thyroid ultrasounds, was granted 510(k) clearance.
- **OLYMPUS'** line of flexible airway mobilescopes was cleared for use.
- **ORTHOFIX MEDICAL's OrthoNext**, a software tool to help healthcare providers during preoperative planning for pediatric orthopedic procedures and deformity analyses, was granted 510(k) clearance.
- **THINK SURGICAL's TSolution One Total Knee Application**, a robotic knee replacement system, was cleared for use with Ortho Development's knee system and implants.
- **TISSUE REGENERATION TECHNOLOGIES' OrthoGold 100**, an extracorporeal shockwave device for temporarily activating connective tissue, increasing blood circulation, and relieving minor aches and pains, was granted 510(k) clearance.
- **WHITERABBIT's WRDensity**, artificial intelligence-based software for measuring breast density, was granted 510(k) clearance.

FDA recalls/warnings

- **ABBOTT/ST. JUDE MEDICAL's Assurity and Endurity** pacemakers were recalled (Class I) because moisture can get in and cause an electrical short and reduce battery life.
- **BOSTON SCIENTIFIC's Vici Venous Stent System and Vici RDS Venous Stent System** were recalled (Class I) because of reports that the stents may migrate or move from where they are initially implanted, possibly requiring another surgery or catheter procedure to retrieve them.
- **Covid-19 –** The FDA issued a warning letter for sales of an unapproved product with fraudulent Covid-19 claims to **Crown Wellness** and to **Covalon Technologies**.
- **GUANGDONG HAIOU MEDICAL APPARATUS –** The FDA sent a letter to healthcare providers recommending that they stop using certain syringes and needles with needle safety devices manufactured by this company until further notice because of reports of some needles detaching from the syringe after injection as well as other needle safety device failures.
- **Mammograms –** The FDA alerted patients and healthcare providers about possible problems with mammograms performed at **Capitol Radiology** in Laurel MD and at **Advanced Women Imaging** in Guttenberg NJ.

- **MEDTRONIC's HeartWare** – The third recall (Class I) of 2021 was issued for this left ventricular assist device (LVAD). This time for issues with the instruction manual.
- **NOVO NORDISK's Tresiba, Levemir, Fiasp, Novolog, and Xultophy** – Almost 1,500 physician samples of these insulin products in Texas were recalled after some of the company's sales representatives experienced power outages due to a winter storm that affected storage temperatures. The recall did not include any commercial products.
- **Smartphones** – The FDA warned consumers to keep their new phone away from their pacemaker or implantable defibrillator because the new batteries may have a stronger magnet that can affect the device operation.

European Regulatory News

- ***Netherlands.*** **NOVARTIS' Zolgensma (onasemnogene abeparvovec)** – Dutch regulators are pushing to get the price of this gene therapy for spinal muscular atrophy cut by 50%, saying that the effectiveness doesn't justify the current $2.1 million price tag and that the drug should not be used unless the price is cut at least that much.
- **ABBOTT's Navitor**, a transcatheter aortic valve replacement (TAVR), was granted a CE Mark.
- **ALBIREO's Bylvay (odevixibat)** – The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended approval of this ileal bile acid transport inhibitor (IBATi) to treat progressive familial intrahepatic cholestasis (PFIC), a rare liver disease.
- **ALMIRALL's Klisyri (tirbanibulin)** – CHMP recommended approval of this microtubule inhibitor as a field treatment for non-hyperkeratotic, non-hypertrophic actinic keratosis.
- **AXONICS' r-SNM**, a second-generation implantable neurostimulator with wireless patient remote control, was granted a CE Mark for use in treating bowel and urinary dysfunction.
- **BAYER's Verquvo (vericiguat)** – CHMP recommended approval of this soluble guanylate cyclase (sGC) stimulator to treat symptomatic chronic heart failure with reduced ejection fraction (HFrEF).
- **BECTON DICKINSON's BD Onclarity HPV** assay was granted a CE Mark for at-home self-collection of a sample to be sent in for analysis to detect HPV.
- **BFORCURE's Chronos Dx**, a portable qPCR thermocycler, was granted a CE Mark for use in Covid-19 testing.
- **BGI GENOMICS' DNA Methylation Detection Kit**, for Human SDC2, ADHFE1, and PPP2R5C genes – which are markers for colorectal cancer – was granted a CE Mark.
- **BIOMÉRIEUX's Vitek MS Prime**, a clinical microbiology mass spectrometry system, was granted a CE Mark.
- **BIOPROJET PHARMA's Ozawade (pitolisant)** – CHMP recommended approval of this selective histamine 3 (H3) receptor antagonist/inverse agonist to treat excessive daytime sleepiness.
- **BLUEBIRD BIO's Skysona (elivaldogene autotemcel)** – CHMP recommended approval of this gene therapy to treat early cerebral adrenoleukodystrophy (CALD).
- **BRISTOL-MYERS SQUIBB's Opdivo (nivolumab) + Yervoy (ipilimumab)** – CHMP recommended approval of this PD-1/CTLA4 inhibitor combination to treat adults with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine-based chemotherapy.
- **CHORDATE MEDICAL's Kinetic Oscillation Stimulation device**, a neuromodulator, was granted an expanded CE Mark allowing it to be used to treat chronic migraines.
- **CORVENT MEDICAL's Respond-19**, a critical care ventilator, was granted a CE Mark.
- **EDGE SURGICAL's EDG Ortho 65mm**, a single-use electronic depth gauge, was granted a CE Mark.
- **GEDEON RICHTER and MYOVANT SCIENCES' Ryeqo (relugolix + estradiol + norethisterone acetate)** – CHMP recommended approval to treat uterine fibroids.
- **INTERSECT ENT's Propel Contour**, a sinus implant for use in sinus surgeries to treat chronic rhinosinusitis, was granted a CE Mark.
- **LIFESIGNALS' LX1550E**, a multiparameter remote monitoring platform, for use in gathering patient physiological data in healthcare settings and at home, was granted a CE Mark.
- **MINDPEAK's BreastIHC**, artificial intelligence-based software for identifying and quantifying breast cancer cells, was granted a CE-IVD Mark.
- **ONE DROP's Blood Glucose Prediction Analysis Engine** for forecasting glucose levels up to eight hours in advance for people with prediabetes, Type 2 diabetes, or gestational diabetes was granted a CE Mark.
- **RHYTHM PHARMACEUTICALS' Imcivree (setmelanotide)** – CHMP recommended approval of this MC4R agonist to treat obesity and the control of hunger associated with genetic deficiencies in the MC4R pathway.
- **TASSO's Tasso-M20**, a self-sampling (at home) blood collection device, was granted a CE Mark.
- **TRANSIT SCIENTIFIC's XO Score**, a scoring sheath platform, was granted a CE Mark.

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

- **ALEXION PHARMACEUTICALS' Ultomiris (ravulizumab)** – NICE is recommending use of this long-acting complement C5 inhibitor to treat proxysmal nocturnal hemoglobinuria. *And* NICE issued draft guidance recommending use in atypical hemolytic uremic syndrome (HUS). All this came after the company agreed to an undisclosed price reduction.

- **BRISTOL-MYERS SQUIBB/CELGENE's Zeposia (ozanimod)** – NICE rejected this oral treatment for relapsing multiple sclerosis in the U.K. and Wales for a second time, saying the effect on slowing disability progression was not clear and it is not cost-effective. Scottish regulators have approved it.

- **JOHNSON & JOHNSON's Erleada (apalutamide)** – In a draft decision, NICE rejected this anti-androgen to treat non-metastatic hormone-relapsed or hormone-sensitive prostate cancer, saying it is not cost-effective.

- **MERCK MSD's Keytruda (pembrolizumab)** – NICE approved use of this PD-1 inhibitor as a first-line treatment for previously untreated metastatic colorectal cancer with a high level of microsatellite instability (MSI-H) or a DNA mismatch repair deficiency (dMMR).

- **PFIZER's Vyndaqel (tafamidis)** – NICE rejected use of this oral transthyretin stabilizer to treat transthyretin amyloidosis patients with cardiomyopathy (ATTR-CM), saying it is not cost-effective.

Regulatory news from other countries

- ***Canada.*** **JOHNSON & JOHNSON's Tecnis Synergy Toric II** – Health Canada cleared this implantable intraocular lens for use.

- ***China***
  - **KINNATE BIOPHARMA's KIN-2787**, a RAF inhibitor, will be developed to treat advanced NSCLC by a Chinese joint venture that includes Orbimed Asia Partners for the Chinese market.
  - **LIANBIO** is partnering with **Xontogeny/Landos** Biopharma to develop and market two programs in Greater China and other regional countries – omilancor (BT-11), a LANCL2 agonist for ulcerative colitis, Crohn's disease, and eosinophilic esophagitis; and NX-13, a NLRX1 agonist for ulcerative colitis and Crohn's disease.

- ***India***
  - **DR. REDDY'S LABORATORIES** bought the exclusive rights in India to **Shenzhen Pregene Biopharma's PRG-1801**, an anti-BCMA CAR T therapy.
  - **MARS MEDICAL DEVICES/SHALBY ADVANCED TECHNOLOGIES** bought California-based **Consensus Orthopedics**, an orthopedic implant company.

2021 FDA Advisory Committees and Other Regulatory Dates of Interest *RED are new since last week*		
Date	**Topic**	**Committee/Event**
Missed PDUFA dates with no new date		
November 25	**Revance Therapeutics' daxibotulinumtoxinA** for glabellar lines	PDUFA date *Delayed by FDA No new date announced*
December tba	**Pfizer and Lilly's tanezumab** to treat moderate-to-severe osteoarthritis pain	PDUFA date missed *No decision announced yet*
January 28	**Amgen's Nplate** (romiplostim) – expanded approval to treat hematopoietic syndrome of acute radiation syndrome	PDUFA date *No decision announced yet*
February 2	**Mallinckrodt's StrataGraft**, a regenerative skin tissue therapy	PDUFA date *Decision delayed due to Covid-19*
April 12	**Fortress Biotech/Avenue Therapeutics' IV tramadol**	PDUFA date *No decision announced yet*
2021 Events		
May tba	**Roche's Esbriet** (pirfenidone) – expanded approval to treat unclassifiable interstitial lung disease	PDUFA date
May 26-27	**2021 FDA Science Forum**	FDA virtual meeting
May 27	**Provention Bio's teplizumab** to treat Type 1 diabetes	FDA's Endocrinologic and Metabolic Drugs Advisory Committee virtual meeting
May 30	**Bristol-Myers Squibb's Zeposia** (ozanimod) for ulcerative colitis	PDUFA date
June 1	**Scynexis' Brexafemme** (ibrexafungerp) for vulvovaginal candidiasis	PDUFA date
June 1	**Myovant Sciences' relugolix** to treat uterine fibroids	PDUFA date
June 3	**Reclassification of three categories of devices** out of unclassified: topical refrigerants (vapocoolants) to Class II, acupressure devices to Class I, and electro-acupuncture stimulators to Class II	FDA's Neurological Devices Advisory Committee virtual meeting
June 4	**Reclassification of three categories of devices** out of unclassified: attention task performance recorders to Class II, optical contour sensing devices to Class I, and plunger-like joint manipulators to Class II	FDA's Neurological Devices Advisory Committee virtual meeting
June 7	**Biogen and Eisai's aducanumab** for Alzheimer's disease	PDUFA date *Extended 3 months by FDA from March 7*
June 7-8	**Morphine milligram equivalents** – current applications and knowledge gaps	FDA Center for Drug Evaluation and Research (CDER) virtual public workshop
June 9	Review of **non-prescription drug** labeling	FDA virtual public workshop
June 9	Discussion of four bulk substances for inclusion on the **503A Bulks List**: choline chloride, oxitriptan, melatonin, and methylcobalamin	FDA's Pharmacy Compounding Advisory Committee virtual meeting
June 10	**Orthopedic device** postmarket review	FDA virtual public workshop
June 10	Discussion of emergency use authorizations for **Covid-19 vaccines for adolescents age 12-17 and age <12**	FDA's Vaccines and Related Biological Products Advisory Committee virtual meeting
June 11	Update on the identification of Medicinal Products (**IDMP**) standards development and implementation	FDA webinar
June 17	**Conversations on Cancer:** National Black Family Cancer Awareness Week	FDA's Oncology Center of Excellence webcast
June 21	**Incyte's topical ruxolitinib** to treat atopic dermatitis	PDUFA date
June 22	Assessment of long-term benefit of **osteoarthritis drugs**	FDA and Arthritis Foundation virtual workshop
June 23	Discussion of a variety of **medical device regulatory issues**	FDA's Office of Medical Device and Radiological Health Operations virtual conference
June 23	**FY2021 generic drug** science and research initiatives	FDA virtual public workshop
June 24	**Incyte's retifanlimab**, a PD-1 inhibitor, as a treatment for locally advanced/metastatic squamous carcinoma of the anal canal (SCAC)	FDA's Oncologic Drugs Advisory Committee virtual meeting
June 30	**Lupin Pharmaceuticals' Solosec** (secnidazole) – expanded approval to treat trichomoniasis	PDUFA date
July tba	**Bayer's finerenone** (BAY-94-8862) for Type 2 diabetes patients with CKD	PDUFA date
July tba	**AbbVie's Rinvoq** (upadacitinib) – expanded use to treat moderate-to-severe atopic dermatitis	PDUFA date
July 2	**Provention Bio's teplizumab** (PRV-031) for preventing/delaying clinical Type 1 diabetes	PDUFA date
July 7	**ChemoCentryx's avacopan** to treat anti-neutrophil cytoplasmic antibody-associated vasculitis	PDUFA date
July 15	**FibroGen's roxadustat** for anemia of CKD in dialysis and non-dialysis patients	FDA's Cardiovascular and Renal Drugs Advisory Committee virtual meeting
July 15	**Biogen and Eisai's aducanumab** for Alzheimer's disease	Institute for Clinical and Economic Review (ICER) review
July 18	**Merck MSD's V114**, a 15-valent pneumococcal conjugate vaccine	PDUFA date

2021 FDA Advisory Committees and Other Regulatory Dates of Interest *RED are new since last week*		
Date	**Topic**	**Committee/Event**
July 20	**Albireo Pharma's odevixibat** (A-4250) to treat pruritus in patients with progressive familial intrahepatic cholestasis (PFIC)	PDUFA date
July 21	**Gastroenterology regulatory endpoints** in eosinophillic gastrointestinal disorders	FDA virtual public workshop
July 22	**Gastroenterology regulatory endpoints** in celiac disease	FDA virtual public workshop
July 25	**Iterum Therapeutics' sulopenem etzadroxil/probenecid** for uncomplicated urinary tract infections	PDUFA date
July 29	**Ardelyx Pharmaceuticals' tenapanor** for hyperphosphatemia in CKD patients on dialysis	PDUFA date *Extended from April 29 by the FDA*
August tba	**Pfizer's TicoVac** for tick-borne encephalitis	PDUFA date
August 12	**Jazz Pharmaceuticals' Xywav** (calcium, magnesium, potassium, + sodium oxybates) – expanded use to treat adult idiopathic hypersomnia	PDUFA date
August 16	**Amgen's sotorasib** for KRAS G12C-mutated NSCLC	PDUFA date
August 17	**Astellas and Seagen's Padcev** (enfortumab vedotin-ejfv) for metastatic/locally advanced urothelial cancer including patients ineligible for cisplatin and who previously received a PD-1/L1 inhibitor	PDUFA date
August 18	**Sensen Bio's vicineum** for non-muscle invasive bladder cancer	PDUFA date
August 18	**Sanofi's avalglucosidase alfa** for Pompe disease	PDUFA date *Extended by FDA by 3 months from May 18*
August 23	**Cara Therapeutics' Korsuva** (difelikefalin, CR-845), a kappa opioid receptor agonist for pruritus in chronic kidney disease patients on dialysis	PDUFA date
August 30	**Kadmon's belumosudil** for chronic graft-versus-host disease after hematopoietic stem cell transplant	PDUFA date *Extended from May 30 by the FDA*
September 15	**Merck MSD's belzutifan** (MK-6482) to treat von Hippel-Lindau disease-associated renal cell carcinoma	PDUFA date
October tba	**Pfizer and OPKO Health's somatrogon** for growth hormone deficiency	PDUFA date
October 10	**Seagen and Genmab's tisotumab vedotin** to treat recurrent/metastatic cervical cancer	PDUFA date
October 17	**Omeros' narsoplimab** for hematopoietic stem cell transplant-associated thrombotic microangiopathy	PDUFA date after FDA extension
October 18	**BeiGene's Brukinsa** (zanubrutinib) – expanded approval to treat Waldenström's macroglobulinemia	PDUFA date
December 21	**Merck MSD's gefapixant** for refractory chronic cough	PDUFA date
2022 Events		
January 28, 2022	**Bristol-Myers Squibb/MyoKardia's mavacamten** for symptomatic obstructive hypertrophic cardiomyopathy	PDUFA date