TRENDS-in-MEDICINE

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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

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

- ✓ ASTRAZENECA's Imfinzi (durvalumab) failed to show a survival benefit in combination with tremelimumab in the Phase III MYSTIC trial in metastatic NSCLC, though an exploratory analysis found survival was extended in patients with high tumor mutation burden.
- ✓ AXOVANT SCIENCES' nelotanserin missed the primary endpoint in a Phase II trial in Lewy body dementia patients with REM sleep behavior disorder (RBD).
- ✓ Biosimilars – The FDA is reclassifying some drugs – particularly insulin – as a biologic in hopes of encouraging biosimilars that will bring down the price.
- ✓ Duodenoscopes – An FDA review found that new cleaning procedures for reprocessed devices are not completely effective.
- ✓ JOHNSON & JOHNSON's Tremfya (guselkumab) beat Novartis' Cosentyx (secukinumab) in a head-to-head Phase III trial in severe psoriasis.
- ✓ MACROGENICS' orlotamab (MGD-009) – Trials were put on hold by the FDA due to liver toxicity.
- ✓ MALLINCKRODT/SPECGX's Roxicodone (abuse-deterrent IR oxycodone) was rejected by the FDA.
- ✓ MARINUS PHARMACEUTICALS' ganaxolone had positive preliminary results in two Phase II trials in postpartum depression.

SHORT TAKES

- 10X GENOMICS is buying **Spatial Transcriptomics**, a Swedish company that develops two-dimensional gene expression technology for tissue samples for high-throughput mRNA analysis.
- ADVAXIS' ADX-NEO – Effective February 8, 2019, Amgen will end its collaboration on this immuno-oncology program.
- AKORN's merger with **Fresenius Kabi** is officially off.
- AMAG PHARMACEUTICALS is buying **Perosphere Pharmaceuticals**, a small biotech that is developing an anticoagulant reversal agent, ciraparantag (PER-977), for all the novel oral anticoagulants as well as enoxaparin (Sanofi's Lovenox), a low molecular weight heparin.
- AMGEN is collaborating with **Entera Bio** on development of oral formulations of up to three biologics for inflammatory diseases.

- AMPIO PHARMACEUTICALS' Ampion – The FDA is requiring a new trial of this low molecular weight fraction of human serum albumin (HSA) in patients with pain from knee osteoarthritis under a special protocol assessment.

- APPLIED GENETIC TECHNOLOGIES' rAAV2tYF-CB-hRS1 – This gene therapy failed in a Phase I/II trial in X-linked retinoschisis (XLRS), failing to show any signs of clinical activity. **Biogen**, which had partnered on the therapy, ended its agreement with AGTC on this and three other discovery programs. AGTC ended development of rAAV2tYF-CB-hRS1.

- ATHENEX's Oraxol (oral paclitaxel) – The company reported results from the second cohort of a Phase Ib trial in combination with Lilly's Cyramza (ramucirumab) in advanced gastric cancer patients who progressed on chemotherapy, saying there were partial responses (PRs) in 3 of 6 patients with the 250 mg/kg dose vs. PRs in 2 of 6 patients on the 200 mg/kg dose in the first cohort.

- AVACTA GROUP is collaborating with **LG Group/LG Chem Life Sciences** on development of Affimer-based drugs for treating inflammatory disorders and on development of two different Affimer PK/ADME modifiers (Affimers that can be fused to other therapeutic proteins to modify certain properties of those biological drug moieties – e.g., serum half-life and tissue localization).

- BAUSCH HEALTH made an offer to buy most of the assets of Synergy Pharmaceuticals, which filed for bankruptcy. This would give Bausch a treatment for chronic idiopathic constipation and irritable bowel syndrome,Trulance (plecanatide).

- BECTON DICKINSON, researchers from the National Institutes of Health (NIH), and a couple of universities reported in ***Science Translational Medicine*** on their collaborative development of a rapid point-of-care diagnostic for detecting Ebola, malaria, Lassa fever, and other pathogens in Africa.

- BELLICUM PHARMACEUTICALS' BPX-601 – Data on 12 patients in a Phase I/II dose-escalation trial in PSCA-positive metastatic pancreatic cancer treated with this CAR T therapy, presented at the European Society for Medical Oncology's (ESMO's) Immuno-Oncology Congress in Geneva, Switzerland, showed 4 of 6 evaluable patients had stable disease, and 2 of these had tumor shrinkage >20%.

- CELLTRION's Remsima (CT-P13, Inflectra in the U.S.) – a biosimilar of **Johnson & Johnson's Remicade** (infliximab) – A study of data on 5,050 Crohn's patients from a French national database, published in the ***Annals of Internal Medicine***, found the two drugs were equivalent in terms of efficacy and safety at one year. The researchers said the findings suggest that the choice in real-life practice should be based on cost alone.

- CONMED, which makes minimally-invasive surgical devices and equipment, is buying Filtration Group's **Buffalo Filter** unit, which has surgical smoke evacuation technology.

- GENSIGHT BIOLOGICS' GS-010 – The company reported sustained quality of life improvements at Week 72 in the 37-patient Phase III REVERSE trial of this gene therapy for Leber hereditary optic neuropathy (LHON).

- GLAUKOS' iStent inject Trabecular Micro-Bypass System – A single-site study, published in the journal ***Ophthalmology and Therapy***, found this glaucoma treatment device implanted during cataract surgery still was beneficial at 3 years post-procedure, with a 37% reduction in intraocular pressure (IOP) and a 68% decrease in medication burden. Overall, 93% of treated patients were able to reduce their medication, with 54% of patients eye-drop free.

- IDERA PHARMACEUTICALS' tilsotolimod – In the ongoing Phase II ILLUMINATE-204 trial of this intra-tumoral TLR9 agonist in combination with Bristol-Myers Squibb's Yervoy (ipilimumab) in unresectable/metastatic melanoma, 32.4% of evaluable patients had a partial response or better, 76.5% of patients achieved disease control, and tumor shrinkage was observed in both injected and uninjected lesions, suggesting an abscopal effect.

- JOHNSON & JOHNSON's Tremfya (guselkumab), an anti-IL-23, beat Novartis' Cosentyx (secukinumab), an anti-IL-17, in the head-to-head Phase III ECLIPSE trial in patients with moderate-to-severe psoriasis. On the primary endpoint of PASI90 at Week 48, Tremfya was superior to Cosentyx (84.5% vs. 70.0%). Tremfya was non-inferior but not superior to Cosentyx on PASI75. The data were presented at the Inflammatory Skin Disease Summit in Vienna, Austria.

- MACROGENICS' orlotamab (MGD-009) – The FDA imposed a partial hold on trials of this CD276/CD3 bispecific in B7-H3-positive cancers, banning new enrollment in both a monotherapy trial and a combination trial with the company's PD-1 inhibitor (MGA-012), but allowing patients already in the trials to continue. The issue is liver toxicity.

- MALLINCKRODT/SPECGX's Roxicodone (immediate-release, abuse-deterrent oxycodone, MNK-812) was rejected as a treatment for severe pain by the FDA, which issued a complete response letter (CRL).

- NEUROCRINE BIOSCIENCES' Ingrezza (valbenazine), a VMAT2 inhibitor, missed the primary endpoint in the Phase IIb T-Force GOLD trial in Tourette syndrome, failing to reduce facial tics significantly more than placebo.

- NEURORX's NRX-101 (D-cycloserine + lurasidone) – In the 6-week, double-blind Phase IIa STABIL-B trial in severe bipolar depression and acute suicidal ideation and behavior (ASIB), presented at the American Congress of Neuropsychopharmacology (ACNP) meeting in Hollywood FL, this combination NMDA antagonist/5-HT2A antagonist showed significantly better improvement on MADRS vs. lurasidone alone.

- NOVO NORDISK is collaborating with **e-Therapeutics** on target discovery in Type 2 diabetes at its new research center in Oxford U.K.

- Opioids – The Centers for Disease Control and Prevention (CDC) reported that fentanyl, not oxycodone, is the country's deadliest drug, with fatal fentanyl overdoses up more than 100% each year from 2013 to 2016 and a factor in ~29% of all overdose deaths in 2016. After fentanyl, 25% of overdose deaths were due to heroin and 18% to cocaine.

- OXFORD BIOTHERAPEUTICS expanded its collaboration with **WuXi Biologics** to include five bispecific antibodies in immuno-oncology.

- Peripheral artery disease – A meta-analysis of 28 trials with a total of 4,663 patients, published in the ***Journal of the American Heart Association***, found that paclitaxel-eluting stents or paclitaxel-coated balloons used in femoral or popliteal arteries were associated with an increased risk of all-cause death at 2 years (7.2% vs. 3.8% for control), with a number needed to harm (NNH) of 29. At 5 years, the risk was even greater – 14.7% vs. 8.1%, with an NNH of 14.

- ROCHE is collaborating with **Merck MSD** on development of a pan-cancer companion diagnostic test for Keytruda (pembrolizumab), a PD-1 inhibitor, based on mismatch repair deficiency (dMMR) in solid tumors.

- SENSORION's seliforant (SENS-111), a histamine H4 receptor antagonist in development to treat vertigo, met the primary tolerability endpoint in the Phase IIa SENS-111-202 trial, showing that it did not affect vigilance or cognitive performance during a motion stimulus – no sedation, impairment of memory, or cognitive impairment.

- SERMONIX PHARMACEUTICALS' lasofoxifene – The FDA accepted an investigational new drug (IND) application for this breast cancer drug, clearing the way for a Phase II trial vs. AstraZeneca's Faslodex (fulvestrant) in postmenopausal women with locally advanced/metastatic ER+/HER2-negative breast cancer with an ESR1 mutation.

- SONIC HEALTHCARE is buying **Aurora Diagnostics**.

- SUNOVION PHARMACEUTICALS and PSYCHOGENICS' SEP-363856 – The results of a Phase II trial in hospitalized schizophrenia patients, presented at the ACNP meeting, showed that this antipsychotic, which is thought to be a TAAR1 activator as well as a 5-HT1A activator, met the primary endpoint, significantly improving the PANSS score vs. placebo at Week 4. The drug also improved overall severity on the CGI-S and improved all positive and negative subscales of PANSS.

- TAURX THERAPEUTICS' LMTX, a protein aggregation inhibitor for treating frontotemporal dementia, was granted orphan drug status by the FDA.

- TRACON PHARMACEUTICALS is partnering with **I-Mab Biopharma** on development of TJD-5, a CD73-targeting antibody, and up to 5 bispecific antibodies.

- XENOTHERAPEUTICS' Xeno-Skin – The FDA approved an IND application, clearing the way for a first-in-man trial of this pig skin transplant for severe burns in humans.

Animal health news

MERCK MSD is buying **Antelliq**, a French company that specializes in digital tracking of livestock and next-generation gadgets for pets.

NEWS IN BRIEF

ASTRAZENECA's Imfinzi (durvalumab)

- This PD-1 inhibitor, both alone and in combination with tremelimumab (a CTLA4 inhibitor), missed the primary endpoint in the 1,118-patient Phase III MYSTIC trial in first-line treatment of metastatic non-small cell lung cancer (NSCLC), failing to improve overall survival vs. chemotherapy alone. The results, presented at ESMO's Immuno-Oncology meeting, also showed:
  - Overall survival was 16.3 months with durvalumab monotherapy, 11.9 months with durvalumab/tremelimumab vs. 12.9 months with chemotherapy in patients with PD-L1 expression ≥25%.
  - In an exploratory analysis of patients with high tumor mutation burden (TMB), overall survival was 11 months with durvalumab monotherapy, 16.5 months with durvalumab/tremelimumab, and 10.5 months with chemotherapy (HR 0.64).
  - In patients with low TMB, overall survival was 8.5 months with durvalumab/tremelimumab, 12.2 months with durvalumab alone, and 11.6 months with chemotherapy. This suggests that TMB might be a way to select patients for treatment with immunotherapy.

- Despite this failure – or maybe partly because of it – AstraZeneca will now test Imfinzi in combination with **AVEO Oncology's Fotivda (tivozanib)** in a Phase III trial in treatment-naïve liver cancer patients.
- Imfinzi will also be tested in a Phase II trial in HPV-related cancers with **MedImmune and Inovio Pharmaceuticals' MEDI-0457** – formerly INO-3112 (an immunotherapy + an IL-12) as part of MD Anderson Cancer Center's Moon Shot effort.
- Is collaborating with **Guardant Health** on development of blood-based companion diagnostics for Imfinzi and Tagrisso (osimertinib), an EGFR inhibitor.

AXOVANT SCIENCES

- **Nelotanserin** missed the primary endpoint in a 34-patient Phase II trial in Lewy body dementia patients who have REM sleep behavior disorder (RBD), failing to reduce the frequency of RBD as measured by sleep laboratory video assessment. The company is giving up on the drug.
- The company licensed the rights to two investigational **gene therapies** (AXO-AAV-GM1 and AXO-AAV-GM2) from the University of Massachusetts Medical School, one for GM1 gangliosidosis (Landing disease) and another for GM2 gangliosidosis (Tay-Sachs and Sandhoff disease).

BRISTOL-MYERS SQUIBB's Opdivo (nivolumab)

- This PD-1 inhibitor will be tested with **Vedanta Biosciences' VE-800**, a gut microbiome booster, in a collaboration in patients with advanced/metastatic solid tumors.
- Expanded results from the CHECKMATE-331 trial in small cell lung cancer were presented at ESMO's Immuno-Oncology Congress, and Opdivo still missed the primary endpoint, failing to significantly prolong overall survival vs. chemotherapy, but there was one new bright spot: the full data showed a durable response (8.3 months vs. 4.5 months with chemotherapy).

EDWARDS LIFESCIENCES

- Is partnering with **Bay Labs** on several projects, including development of artificial intelligence-powered algorithms for detecting heart disease.
- Sapien 3. A federal jury found that this transcatheter aortic valve replacement (TAVR) infringes on a Boston Scientific patent and awarded Boston Scientific damages. Edwards plans to appeal. The jury also ruled that Boston Scientific's Lotus TAVR does not infringe Edwards patents.

LILLY

- Is collaborating with **AC Immune** on research and development of tau aggregation inhibitors to treat Alzheimer's disease and other neurodegenerative diseases using AC Immune's Morphomer technology and, at least initially, focusing on ACI-3024.
- Expanded its collaboration with **Evidation Health** on health data from smartphones and wearables.
- **and Incyte's Olumiant (baricitinib)** was granted fast track status by the FDA as a treatment for systemic lupus erythematosus.

MARINUS PHARMACEUTICALS' ganaxolone

The company reported positive preliminary results from two Phase II trials of this $GABA_A$ modulator in women with postpartum depression (PPD), though optimal dosing has not yet been determined.

- In the MAGNOLIA trial of IV administration, the high dose (140 µg/kg/h) showed a clinically meaningful 5.6-point reduction in HAM-D17 vs. placebo at 48 hours, and it was durable through Day 34. In addition, 75% were responders (≥50% reduction in HAM-D17) at Day 34, and 50% of patients achieved remission from depression (HAM-D17 ≤7) at Day 34.
- In the ongoing AMARYLLIS trial of an oral formulation, data on the most recent dose cohort showed a HAM-D17 reduction of 13.2 points at Day 28 and a 15.7 point reduction at Day 36.
- In both trials the drug appeared safe and well-tolerated with no serious adverse events.

MERCK KGAA

- Licensed a cloud-based artificial intelligence proteome platform for screening of protein-drug interactions from **Cyclica**.
- M7824, an investigational treatment for biliary tract cancer, was granted orphan drug status by the FDA.

Predictions for 2019

The CEO of Call9, a telehealth platform for skilled nursing facilities, offered some not very surprising healthcare industry predictions for 2019:

- Value-based care arrangements will provide opportunity for bipartisanship in 2019.
- Tech-related services will increase.
- Data will transform how providers make decisions.

- Payors will embrace technology innovation more than ever before.
- Private partnerships with healthcare providers will increase.

TARGET PHARMASOLUTIONS

The company announced partnerships with:

- **Gilead Sciences** – a new partnership in hepatitis B virus (TARGET-HBV) and non-alcoholic steatohepatitis (NASH) – TARGET-NASH.
- **Bristol-Myers Squibb** – an expanded partnership that includes inflammatory bowel disease (TARGET-IBD).

REGULATORY NEWS

Regulatory tidbits

- Antitrust. The state-led antitrust lawsuits into alleged price-fixing of generic drugs has expanded to include at least 16 companies and 300 drugs.
- Biomarkers. The FDA issued draft guidance on the type of evidence the FDA will accept to support development of a biomarker.
- Data integrity. Calling data integrity a "core value" and an integral part of compliance with current good manufacturing practice (cGMP), FDA Commissioner Scott Gottlieb, MD, announced an update to 2016 guidance on data integrity focused on evaluating proper storage and handling, identifying lapses, ensuring consistent awareness and commitment, and more.
- Digital health tools. The FDA issued a report on the benefits and risks of digital health tools ***not*** regulated by the FDA as medical devices, concluding that, in general, the benefits of the products "generally outweigh the risks to patients." The FDA will publish a report biennially. The types of software functions that were reviewed include: e-prescribing, mindfulness apps, some electronic health records (EHRs), lab test results display/storage, clinical decision support software such as those that identify drug interactions.
- Drug prices. A Senate bill, sponsored by Richard Blumenthal (D-CT) and three other Democratic Senators, was introduced in the Senate that would allow the Department of Health and Human Services (HHS) to force drug companies to rebate to payors and patients any excess charge for a drug if HHS determines the price increase was unjustifiable. Or, HHS could make the drug available at the old price.
- Generic drugs
  - The House of Representatives approved a bipartisan bill that would allow HHS to reclassify drugs and recover rebates when pharmas intentionally misclassify drugs as generics under Medicaid.
  - The FDA withdrew a proposed rule that would have allowed generic drug companies to update the label on their generic drug with safety information without prior review and approval by the FDA, just as brand companies are allowed to do with branded drugs.
- Medical device tax. Legislation was introduced in the House that would impose a 5-year moratorium on the medical device tax (until the end of 2024).
- Obamacare. A federal judge in Texas struck down the Affordable Care Act as unconstitutional, but his ruling is likely to be appealed.

Biosimilars

FDA Commissioner Dr. Gottlieb, in announcing new actions aimed at promoting biosimilars, noted that biosimilar progress has "disappointed some," but added that he is "not discouraged," saying, "I believe it will take time for this market to mature…This is a dynamic market, and we'll continue to address potential barriers to competition as they emerge, including in partnership with colleagues at the Federal Trade Commission."

- The FDA issued two new draft guidance documents, and Dr. Gottlieb emphasized one "critical" issue in them: "Companies using – and sometimes abusing – limited distribution systems," sometimes in connection with a REMS, to delay or derail biosimilar sponsor access to reference product samples. He said, "Too many branded products are still misusing these programs as rhetorical smokescreens to hide anti-competitive behavior. We're not going to be partners to these deceptions."

  As a start, the FDA will now, on request, review study protocols submitted by biosimilar applicants, determine if they comply with REMS, and issue a letter to the brand drug company informing it that the FDA won't consider it a violation of the REMS to provide the biosimilar sponsor with a sufficient quantity of the reference product to perform testing necessary to support its biosimilar application.
- The FDA also released two guidance documents on how the FDA will handle transitioning certain biological products currently approved as drugs to biologics – ***including insulin and human growth hormone***. And, no, that doesn't mean the brand gets longer exclusivity. Drugs moved to the biologics category will be removed from the FDA's Orange

Book on March 23, 2020, and listed in the Purple Book. Supplemental new drug applications (sNDAs) in process will be converted to supplemental biologics license applications (sBLAs), but that also doesn't mean they will get 12 years of exclusivity.

Compounding

FDA Commissioner Dr. Gottlieb said the Agency is concerned that the Agency is still seeing "far too much unsafe activity" by compounding pharmacies and outsourcing facilities. He announced:

- New draft guidance that updates the FDA's policies related to outsourcing facilities, with the goal of making it more feasible for compounding pharmacies to become outsourcing facilities. In particular, the action is aimed at compounding pharmacies that handle products at high risk of contamination – e.g., compounding done on a large scale, drugs that must be sterile, and products that require many manual manipulations. The new policies include revisions related to release testing, stability testing, and beyond-use dating plus policies that differentiate between production of sterile and non-sterile drug products.
- Plans soon to further define what substances can be used in compounded products by traditional compounders.
- The addition of 2 products to the list of drugs that cannot be compounded: bromocriptine mesylate for prevention of lactation and ondansetron (>16 mg) for nausea prevention.

FDA approvals/clearances

- AMGEN's Nplate (romiplostim) was granted expanded approval to treat immune thrombocytopenia (ITP) in children age ≥1.
- CONTEGO MEDICAL's Vanguard IEP, a peripheral balloon with an embolic protection function, was granted 510(k) clearance for use in treating peripheral artery disease (PAD).
- HOLOGIC's Omni hysteroscope was granted 510(k) clearance.
- MARINER ENDOSURGERY's LaparoGuard, an augmented reality navigation system that warns surgeons of potential problem areas during minimally-invasive procedures.
- MAYNE PHARMA's Tolsura (SUBA-itraconazole) was approved to treat adults infected with aspergillosis, blastomycosis, or histoplasmosis.
- NOVO NORDISK's Novoeight was granted expanded approval to include use as an on-demand therapy in adult and pediatric patients with hemophilia A.
- NUVASIVE's Monolith Corpectomy System was granted expanded 510(k) clearance for use in cervical corpectomy procedures.
- PEAR THERAPEUTICS' reSET-O, a mobile medical app for helping to retain opioid use disorder patients in outpatient treatment programs, was granted 510(k) clearance.
- THERMO FISHER SCIENTIFIC's QMS Plazomicin Immunoassay, for helping to determine the appropriate dose of plazomicin, was cleared for use.

FDA recalls/warnings

- BAROX, a South Korean manufacturer of over-the-counter drugs, received a warning letter about violation of cGMP, after an inspection found there was no formalized quality control. In fact, the inspectors found "all" of the company's employees were uninformed on cGMP requirements.
- Duodenoscopes – Current procedures for reprocessing these devices are not proving sufficient. The FDA issued a Safety Alert with the preliminary results of FDA-mandated post-market studies of the safety of reprocessing these devices, saying the studies are showing higher than expected contamination rates with reprocessing, with ≤6% of devices classified as reprocessing failures, and half of these were contaminated with "high concern" organisms.

  All three U.S. duodenoscope manufacturers – Olympus, Fujifilm, and Pentax – were required to conduct two post-market surveillance studies (one on contamination rates and one on how well hospital staff could follow the reprocessing instructions) to determine whether healthcare facilities were able to properly clean and disinfect the devices. However, none of the companies complied, and earlier this year, the FDA sent each of them a warning letter. That prompted the companies to get the studies done and led to these results.

  Jeffrey Shuren, MD, JD, director of the FDA's Center for Devices and Radiological Health (CDRH), said the companies are currently conducting root cause analyses to understand these preliminary results. And he said the FDA is advising hospitals and healthcare facilities that use duodenoscopes to ***meticulously*** follow manufacturer reprocessing instructions and consider implementing supplemental reprocessing measures.

  What's new is that the FDA is now also recommending that hospital staff carefully inspect a component of the duodenoscope that is difficult to clean, the elevator recess, and to repeat cleaning if any soil or debris is visible. The FDA is also urging users to return the duodenoscopes to the manufacturer at least once a year for inspection, servicing, and maintenance.

However, the FDA has concluded that reprocessing current devices is not safe enough, and the Agency has been working with developers on new product designs, including disposable components. And Dr. Shuren added that the Agency is willing to bring criminal actions – as it did with Olympus – if manufacturers don't follow the rules about reporting infections with these devices.

- GE HEALTHCARE's CareScape R860 ventilator safety guards were recalled (Class I) because of a manufacturing defect that could cause the device to disconnect from a patient's breathing circuit.
- OLYMPUS/OLYMPUS MEDICAL SYSTEMS pled guilty to charges that it failed to file reports with the FDA about infections related to its duodenoscopes and agreed to pay an $80 million fine and forfeit another $5 million.
- ZHEJIANG HUAHAI, a Chinese company at the heart of the worldwide "sartan" contamination problem, received a strongly worded warning letter from the FDA for failing to detect the contaminant (a potential carcinogen) in its active pharmaceutical ingredients (APIs) when a customer complained several years ago.

European Regulatory News

- AOP ORPHAN PHARMACEUTICALS' Besremi (ropeg-interferon alfa-2b) – The European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) recommended approval of this treatment for polycythemia vera without symptomatic splenomegaly.
- BRISTOL-MYERS SQUIBB's Sprycel (dasatinib) – CHMP recommended expanded pediatric approval to include treatmetn of newly diagnosed Ph+ acute lymphoblastic leukemia (ALL) in combination with chemotherapy.
- CHIESI FARMACEUTICI's Trimbow (beclometasone + formoterol + glycopyrronium) – CHMP recommended expanded approval for maintenance therapy in chronic obstructive pulmonary disease patients not adequately treated with the combination of an inhaled corticosteroid and a long-acting $beta_2$-agonist or a combination of a long-acting $beta_2$-agonist and a long-acting muscarinic antagonist.
- CLOVIS ONCOLOGY's Rubraca (rucaparib) – CHMP recommended expanded approval to include maintenance of relapsed ovarian cancer.
- DIPHARMA's Miglustat Dipharma (miglustat) – CHMP recommended approval to treat mild-to-moderate type 1 Gaucher disease.
- Fosfomycin – (e.g., Zambon's Monuril) – At the request of German authorities, the EMA started a review of drugs containing this antibiotic to determine if the marketing authorizations should be amended because of increasing resistance to antibiotics.
- GE HEALTHCARE's Rapiscan (regadenoson) – CHMP recommended approval for use in fractional flow reserve (FFR) measurement of a single coronary artery during angiography when repeated FFR measurements are not anticipated.
- JOHNSON & JOHNSON/JANSSEN's Simponi (golimumab) – CHMP recommended expanded approval for use in prefilled syringes to treat juvenile arthritis.
- MEDAC GESELLSCHAFT FÜR KLINISCHE SPEZIALPRAPARATE's Trecondi (treosulfan) – CHMP recommended approval for conditioning prior to an allogeneic hematopoietic stem cell transplant.
- NUVECTRA's Algovita, a spinal cord stimulation system, was granted full-body MRI-conditional approval.
- Omega-3 fatty acids – The EMA concluded that omega-3 fatty acids are ***not*** effective in preventing further cardiac problems in patients who have had a heart attack – and revoked the approval of products by Pfizer, Mylan, Teva, and BASF/Pronova BioPharma. However, the products can still be used to reduce triglycerides. *There was no mention of Amarin Pharma's Vascepa (icosapent ethyl 4 g/day).*
- PARI PHARMA's Tobramycin PARI, a new formulation of nebulized tobramycin, was approved to treat chronic pulmonary infections due to *Pseudomonas aeruginosa* in cystic fibrosis patients age ≥6.
- PFIZER's Zirabev (bevacizumab) – a biosimilar of Roche's Avastin – CHMP recommended approval to treat metastatic colorectal cancer, metastatic breast cancer, and several other cancers.
- PORTOLA PHARMACEUTICALS' Ondexxya (andexanet alfa) – CHMP extended its review of this Factor Xa reversal agent until February 28, 2019, and requested more information from the company.
- PREDICTIMMUNE's PredictSURE, a prognostic biomarker test for inflammatory bowel syndrome, was granted a CE-IVD Mark.
- SHIONOGI
  - Lusutrombopag Shionogi (lusutrombopag) – CHMP recommended approval of this TPO receptor agonist to treat severe thrombocytopenia in adults with chronic liver disease undergoing invasive procedures.

- Rizmoic (naldemedine) – CHMP recommended approval of this peripherally-acting mu-opioid receptor antagonist to treat opioid-induced constipation.

- TAKEDA's Adcetris (brentuximab vedotin) – CHMP recommended approval to treat patients with previously untreated CD30+ Stage IV Hodgkin's lymphoma in combination with AVD (doxorubicin, vinblastine, and dacarbazine).

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

- AKCEA THERAPEUTICS and IONIS PHARMACEUTICALS' Tegsedi (inotersen) – NICE released draft guidance recommending against use of this once-weekly treatment for hATTR, saying it is not cost-effective at ~$7,500 per injection despite an undisclosed discount, and the long-term benefits are not known. The report is open for comments until January 9, 2019.

- ALNYLAM PHARMACEUTICALS' Onpattro (patisiran) – NICE released draft guidance recommending against use of this RNAi treatment for hATTR patients with Stage 1 or 2 polyneuropathy, saying it is not cost-effective at ~$9,000 per infusion every 3 weeks, despite an undisclosed discount, and the long-term benefits are not known. The report is open for comments until January 9, 2019.

- AXONICS MODULATION TECHNOLOGIES' r-SNM – Among the findings in the NICE briefing review of this rechargeable sacral neuromodulation device for urinary incontinence and bowel dysfunction were:
  - Longer-term data would be nice, as would a head-to-head comparison with Medtronic's InterStim II, a non-rechargeable device.
  - The reduction in replacement procedures (every 15+ years vs. 3-5 years for InterStim II) was a key factor in the positive opinion on this device.
  - Cost comparable to InterStim II.
  - The smaller size of r-SNM might make the device more comfortable for patients, especially smaller patients.
  - A broader MRI-head compatibility label.

Regulatory news from other countries

- *Canada.* VERTEX PHARMACEUTICALS' Orkambi (ivacaftor + lumacaftor) was granted expanded approval by Health Canada for use in patients age 2-5 with cystic fibrosis who have 2 copies of the F508del CFTR mutation.

- *China.* LILLY is partnering with Parexel, a contract research organization, to build a clinical research learning and development program in China.

- *India.* MERIL LIFE SCIENCES' MyVal, a TAVR, was approved for use in high-risk patients and those unwilling to undergo open heart surgery.

2018 FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
Dec. 17-18	Strategies to increase the availability of **naloxone** products in the community	FDA's Anesthetic and Analgesic Drug Products Advisory Committee meeting jointly with the Drug Safety and Risk Management Advisory Committee
December 18	**ADMA Biologics' Bivigam** (immunoglobulin IV, human) for primary humoral immunodeficiencies	PDUFA date *FDA review extended from October 25*
December 20	**Jazz Pharmaceuticals' solriamfetol** (JZP-110) for excessive sleepiness in patients with narcolepsy or sleep apnea	PDUFA date
December 21	**Shire's prucalopride** (SHP-555) for chronic idiopathic constipation	PDUFA date
December 22	**Shire's calaspargase pegol** (SHP-663) for acute lymphoblastic leukemia	PDUFA date
December 26	**Braeburn Pharmaceuticals' CAM-2038** for treating opioid use disorder	PDUFA date
December 28	**Merck MSD's Keytruda** (pembrolizumab) to treat Merkel cell carcinoma	PDUFA date
December 29	**Bristol-Myers Squibb's Sprycel** (dasatinib) for Ph+ ALL	PDUFA date

2019 FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
January 5	**Acorda Therapeutics' Inbrija** (inhaled levodopa) for Parkinson's disease	PDUFA date *Extended from October 5, 2018, by the FDA*
January 11	**Takeda's Uloric** (febuxostat) – cardiovascular safety of this gout treatment	FDA's Arthritis Advisory Committee meeting jointly with the Drug Safety and Risk Management Advisory Committee
January 14	**Exelixis' Cabometyx** (cabozantinib) for expanded use to treat advanced hepatocellular carcinoma	PDUFA date
January 16	**Amgen** and **UCB's Evenity** (romosozumab), an anti-sclerostin to treat osteoporosis in postmenopausal women	FDA's Bone, Reproductive, and Urologic Drugs Advisory Committee
January 17	**Sanofi** and **Lexicon Pharmaceuticals' Zynquista** (sotagliflozin), an SGLT1/2 inhibitor for adjunctive treatment of Type 1 diabetes	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
January 28	**Sanofi Pasteur's Fluzone**, a quadrivalent flu vaccine for children age 6-35 months	PDUFA date
January 29-30	Premarket submissions for management of **cybersecurity** in medical devices	FDA public workshop
January 31	**Alkermes' ALKS-5461** (samidorphan + buprenorphine) for major depressive disorder	PDUFA date
February 2	**Evolus** and **Daewoong Pharmaceutical's prabotulinumtoxinA** (DWP-450) for glabellar lines	PDUFA date
February 6	**Sanofi's Cablivi** (caplacizumab) for aTTP	PDUFA date
February 12	Discussion of the safety and effectiveness of **transvaginal mesh** for pelvic organ prolapse repair – and consideration of additional regulatory actions	FDA's Obstetrics and Gynecology Devices Advisory Committee
February 13	**Motif Bio's ilaprim**, an antibiotic for acute bacterial skin and skin structure infections (ABSSSI)	PDUFA date
February 15	**Bausch Health's Duobrii** (halobetasol propionate + tazarotene) for psoriasis	PDUFA date
February 18	**Alexion Pharmaceuticals' ALXN-1210** for treating paroxysmal nocturnal hemoglobinuria	PDUFA date
February 21	**Stemline Therapeutics' Elzonris** (tagraxofusp, SL-401) for treating blastic plasmacytoid dendritic cell neoplasm	PDUFA date
February 25	**Bausch Health/Bausch + Lomb's submicron loteprednol etabonate** for pain/inflammation after eye surgery	PDUFA date
March tba	**Novartis' siponimod** for secondary progressive multiple sclerosis	PDUFA date
March 11	**Regeneron Pharmaceuticals** and **Sanofi's Dupixent** (dupilumab), expanded approval to treat adolescents age 12-17 with atopic dermatitis	PDUFA date
March 12	**Roche's Tecentriq** (atezolizumab) as a first-line treatment for PD-L1+ metastatic triple-negative breast cancer in combination with Celgene's Abraxane (nab-paclitaxel)	PDUFA date
March 14	**Aerie Pharmaceuticals' Roclatan** (netarsudil/latanoprost) for glaucoma	PDUFA date

2019 FDA Advisory Committees and Other Regulatory Meetings – continued (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
March 18	**Roche's Tecentriq** (atezolizumab) for first-line treatment of extensive-stage small cell lung cancer in combination with carboplatin and etoposide	PDUFA date
March 19	**Sage Therapeutics' Zulresso** (IV brexanolone, SAGE-547) for postpartum depression	PDUFA date *FDA review extended by 3 months to March 19, 2019*
March 21	**Glenmark Pharmaceuticals' Ryaltris** (olopatadine + mometasone furoate) for seasonal allergic rhinitis	PDUFA date
March 22	**Sedor Pharmaceuticals' IM/IV Captisol-Enable Fosphenytoin** (fosphenytoin sodium and sulfobutylether beta-cyclodextrin sodium for injection) to treat generalized tonic-clonic status epilepticus and seizures during neurosurgery	PDUFA date
March 23	**Palatin Technologies' bremelanotide** for hypoactive sexual desire	PDUFA date
April 6	**Karyopharm Therapeutics' selinexor** for refractory multiple myeloma	PDUFA date
April 28	**Regeneron Pharmaceuticals** and **Sanofi's Praluent** (alirocumab) label claim for cardiovascular risk reduction	PDUFA date
May 1	**Sanofi Pasteur's Dengvaxia** for dengue fever	PDUFA date
May 13	**Regeneron Pharmaceuticals** and **Bayer's Eylea** (aflibercept) expanded approval to treat diabetic retinopathy	PDUFA date
May 21	Discussion of FDA's proposed rule changes for **outsourcing facilities and compounding pharmacies**	FDA public meeting
June 10	**Xeris Pharmaceuticals' liquid glucagon auto-injector** for severe hypoglycemia	PDUFA date