TRENDS-in-MEDICINE

July 29, 2012

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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SHORT TAKES

- **ABBOTT's Xpert** – A study published in ***Catheterization and Cardiovascular Interventions*** found that this self-expanding bare metal infrapopliteal stent eased pain and was safe to use for blocked leg arteries. At 1 year, 78% of patients were alive without amputation.

- **AETERNA ZENTARIS' AEZS-130** – The company asked the FDA for fast track status for this investigational test to diagnose growth hormone deficiency and expects to submit it to the FDA in 1Q13 if fast track status is granted.

- **BAYER** reportedly is in talks to sell its blood glucose meters business. Among the rumored potential buyers are **Sanofi** and **Panasonic**, though Panasonic denied it is interested in the business.

- **BG MEDICINE's Architect Galectin-3** test was submitted to the FDA for 510(k) clearance. If approved, it would run on **Abbott's Architect** immunochemistry instrument platform to measure levels of galectin-3, a protein that leads to heart failure.

- **BIOCON's itolizumab** – ***Reuters*** reported that this Indian company plans to submit this psoriasis drug to regulators in the near future and to commercialize it by the end of its 2013 fiscal year.

- **Blindness** – Research published in the journal ***Neuron*** describes success restoring sight in mice born with blindness similar to inherited and age-related blindness affecting humans with the use of a chemical called AAQ that makes the cells in the retina sensitive to light. The effect of the chemical is temporary but may offer new avenues for blindness research.

- **FRESENIUS KABI** acquired **Fenwal**, a global blood technology company focused on transfusion medicine and cell therapies.

- **GALENICA's Injectafer (ferric carboxymaltose)** – The FDA withheld approval of this IV iron because of manufacturing issues at the **Luitpold Pharmaceuticals**' factory where it would be made.

- **GILEAD SCIENCES' elvitegravir** – The company said a Phase III trial in HIV found this QD integrase inhibitor was non-inferior to **Merck's Isentress** (raltegravir), which is BID. *Remember elvitegravir is one component of **Gilead's Quad** for HIV.*

- **GLAXOSMITHKLINE and LIGAND PHARMACEUTICALS' Promacta (eltrombopag)** was granted priority review by the FDA as a treatment for thrombocytopenia in patients with chronic hepatitis C.

- **HALO HEALTHCARE** signed a license agreement with the University of North Dakota to develop biomarkers for the early detection of breast cancer using breast nipple aspirate fluid.

- **IDENIX PHARMACEUTICALS' IDX-719**, an investigational NS5A inhibitor to treat hepatitis C, was granted fast track status by the FDA.

- **IMMUNOCELLULAR THERAPEUTICS' ICT-121 –** The FDA gave the company permission to start a Phase I trial in up to 20 patients with this dendritic-cell-based vaccine in recurrent glioblastoma multiforme.

- **iROBOT's RP-VITA –** The company unveiled a new "telemedicine robot" in partnership with **InTouch Health**, which makes in-hospital robots. RP-VITA is designed to help patients with health emergencies get more rapid treatment from specialists, especially at night.

- **KIPS BAY MEDICAL's eSVS Mesh system –** The company filed a second investigational device exemption (IDE) application with the FDA for this system that supports leg veins transplanted in patients undergoing a coronary artery bypass graft (CABG). If approved, the company plans to add four U.S. sites to an ongoing trial of the device in Europe.

- **LILLY and KOWA PHARMACEUTICALS' Livalo (pitavastatin) –** Although statins generally pose a risk when given with a protease inhibitor, a single-center, open-label study in healthy adults found little potential for interaction between Livalo and **Pfizer's Prezista** (darunavir boosted with ritonavir) because Livalo, unlike most other statins, does not use the cytochrome P450 (CYP450) pathway.

- **MEDIVATION and ASTELLAS' enzalutamide (MDV-3100) –** The FDA granted priority review to this oral investigational treatment for men with castration-resistant prostate cancer post-docetaxel chemotherapy.

- **NOVAVAX's influenza vaccine –** The company said that a second Phase II trial was positive, demonstrating safety and starting an immune response. Novavax hopes to get accelerated approval.

- **PLURISTEM THERAPEUTICS' PLacental eXpanded (PLX) cells –** The company said it is preparing to submit an application to the FDA within the next month seeking approval as an orphan drug treatment for anemia caused by abnormal bone marrow.

- **ROCHE's Actemra/RoActemra (tocilizumab) –** The company announced that subcutaneous Actemra met the primary end-point in a second trial, the BREVACTA trial, in rheumatoid arthritis, and Roche plans to submit this new formulation to regulatory authorities globally. At 24 weeks, patients with subcutaneous Actemra had significantly higher ACR20 scores and less joint worsening by x-ray than placebo, and no new safety issues were reported.

- **THROMBOGENICS' Jetrea (ocriplasmin) –** The FDA's Dermatologic and Ophthalmic Drugs Advisory Committee voted 6-3 that additional studies are ***not*** needed to evaluate the safety of the effect of Jetrea on the retina (eye pain and swelling) before the drug is approved.

NEWS IN BRIEF

ACORDA THERAPEUTICS and BIOGEN IDEC's Ampyra/Fampyra (dalfampridine) – new seizure warning

The FDA issued a new, updated warning on seizures for this drug to improve walking in patients with multiple sclerosis. The Agency said:

- Kidney function should be monitored before and at least annually during the drug's use.
- Seizures can occur in patients starting the medicine at normal doses, with most seizures occurring in patients with no seizure history.
- Patients who miss a dose should not take an extra dose because that can increase the seizure risk.

CUTERA's GenesisPlus Laser System – slammed by FDA for unapproved claims

The FDA sent Cutera a warning letter, saying that the company was improperly marketing this device. GenesisPlus is approved for the temporary increase of clear nail in patients with onychomycosis, but the company's website touted it as a treatment for skin rejuvenation and for onychomycosis, neither of which is an approved indication.

Furthermore, the FDA said Cutera modified the spot size for the device without getting FDA clearance. A 1 mm spot size was cleared, but the specifications on the website are 1.5 and 5 mm. The FDA wants the violations corrected and a plan for preventing similar violations from occurring in the future.

Endocannabinoids – new life for this weight-loss class

Sanofi's Acomplia (rimonabant) was rejected by the FDA and withdrawn from the European market due to psychiatric side effects (depression and anxiety). Now, researchers at the National Institute on Alcohol Abuse and Alcoholism have taken another endocannabinoid (SLV319) and structurally modified it so that it doesn't cross the blood brain barrier, just affecting

cannabinoid receptors throughout the body. In animal studies published in ***Cell Metabolism***, the new agent, JD-5037, produces weight loss without causing anxiety or depression. Human clinical trials are next.

EXELIXIS' cabozantinib – investigators start new trials

The company announced that two investigator-sponsored trials have been initiated with this combination MET/VEGFR2/RET inhibitor.

- Memorial Sloan-Kettering Cancer Center started a 25-patient Phase II trial of cabozantinib 60 mg/day in non-small cell lung cancer (NSCLC) patients who test positive for gene fusions that activate RET, with the primary endpoint overall survival.
- Massachusetts General Hospital (MGH) started a Phase I trial in patients with relapsed/refractory multiple myeloma to assess safety, tolerability, and preliminary activity. The first cohort will get 40 mg/day. Based on the safety results, a second cohort will test either 20 mg or 60 mg/day.

International AIDS Conference news

- **GILEAD SCIENCES' cobicistat.** This "booster" drug that is part of Gilead's **Quad** for HIV showed similar efficacy at a full dose – and similar side effects – as **Abbott's Norvir** (ritonavir). At 48 weeks, 85% of cobicistat patients had undetectable HIV RNA vs. 87% ritonavir patients.
- **MERCK's Isentress (raltegravir).** Standard therapy for HIV/TB co-infected patients is rifampin + **Gilead's Viread** (tenofovir) + (lamivudine, 3TC) + **Bristol-Myers Squibb's Sustiva** (efavirenz). However, the 24-week Phase II ANRS 12180 REFLATE TB trial conducted in France and Brazil found that substituting raltegravir for efavirenz was just as effective but with fewer side effects, especially central nervous system toxicity, and less resistance and less risk of teratogenicity. The efficacy of raltegravir was similar to that of efavirenz (76%-78% vs. 63%).
- **PaMZ.** A small study (NC-001), presented at the meeting and simultaneously published in ***The Lancet***, found this three-drug combination – an approved antibiotic (not approved in TB), an approved TB drug, and the Global Alliance for TB Development's PA-824 (an investigational bicyclic nitroimidazole) – to be very promising as a new tuberculosis treatment, even in patients resistant to the two commonly used agents. However, it still needs to be tested in a larger Phase III trial.
- **VIIV's dolutegravir.** A 48-week, double-blind study found a 50 mg QD dose of this investigational integrase inhibitor was non-inferior to **Merck's Isentress** (raltegravir), which is BID, in antiretroviral-naïve HIV patients when co-administered with 2 NRTIs. Safety was comparable, and there were no discontinuations for renal events.

MERCK

- **CHIMERIX's CMX-157.** Merck licensed worldwide rights to this nucleoside reverse transcriptase inhibitor for HIV that is in a Phase I trial.
- **YAMASA's EFdA.** Merck also licensed this nucleoside reverse transcriptase inhibitor for HIV.
- **MK-1439.** Merck plans to start Phase II trials of this next-generation non-nucleoside reverse transcriptase inhibitor for HIV.

PFIZER

- **Lyrica (pregabalin).** The company announced positive top-line results of two studies requested by regulators. In an FDA-requested postmarketing study in >200 healthy men, Lyrica did ***not*** affect reproductive function (sperm production). In a trial requested by the European Medicines Agency (EMA), Lyrica had a low rate of withdrawal-related symptoms in generalized anxiety disorder.
- **Cyklokapron (IV tranexamic acid).** A study published in the ***Journal of Bone and Joint Surgery*** found that a single intraoperative dose is significantly more effective than placebo in reducing blood loss in patients undergoing minimally-invasive total knee arthroplasty (TKA).

ROCHE/GENENTECH

- **Lucentis (ranibizumab).** The FDA's Dermatologic and Ophthalmic Drugs Advisory Committee voted unanimously (10-0) to recommend approval of the 0.3 mg dose of Lucentis to treat diabetic macular edema (DME). The panel also voted 8-2 to recommend approval of the 0.5 mg dose. The PDUFA date is August 10, 2012.
- **Tarceva (erlotinib).** A trial found that first-line treatment of advanced non-small cell lung cancer with Tarceva was not a reasonable choice for general, unselected patients where chemotherapy is the standard treatment. In this trial, patients started with Tarceva, followed by cisplatin-gemcitabine.

SANOFI

- Tetravalent dengue vaccine was found effective and safe in a trial of 4,000 children in Thailand. If approved by regulators, this would be the first preventive treatment for this mosquito-borne disease. However, the vaccine protected against only three of the four strains of the virus.
- FDA inspectors found "significant objectionable conditions" at Sanofi's vaccine plants in Canada and France and summoned the company's vaccine head and other senior executives to a meeting at the FDA to discuss the issues and the steps the company is taking to resolve them. The FDA cited 24 violations of good manufacturing practices.

REGULATORY NEWS

FDA asked to restrict opioids

Public Citizen, along with a group of doctors, public health officials, and other pain experts, filed a Citizen Petition with the FDA asking the Agency to:

- Change the labeling directions for use to provide clearer guidance to doctors on how extended-release painkillers should be used.
- Reduce claims that pharmas can make about high doses.
- Limit non-cancer use of opioids to patients with "severe" pain.
- Limit the maximum dose to ~100 mg/day for ≤90 days for non-cancer pain.
- Restrict marketing aimed at non-cancer patients. In particular, this would prevent advertising these drugs as safe for long-term use.

FDA approvals/clearances

- **AMARIN's Vascepa (icosapent ethyl, AMR-101)** – This nearly pure EPA prescription omega-3 fatty acid (fish oil) was approved to treat high triglycerides, and the company is expected to launch it in 1Q13. The big question remaining is whether or not the FDA will determine that Vascepa is a new chemical entity (NCE); that decision is expected by August 17, 2012. Without NCE status, Amarin would have shorter marketing exclusivity, though Vescepa still would be patent protected.
- **CORINDUS VASCULAR ROBOTICS' CorPath 200**, a robot-assisted device to aid in percutaneous coronary interventions (PCIs), received 510(k) clearance. The device would reduce the cardiologist's radiation exposure.
- **FOREST LABORATORIES and ALMIRALL's Tudorza Pressair (aclidinium bromide)** – This BID, inhaled, long-acting, muscarinic 3 receptor agonist was approved by the FDA to treat chronic obstructive pulmonary disease (COPD).
- **HORIZON PHARMA's Rayos/Lodotra (delayed-release, low-dose prednisone)** – The FDA approved expanded uses in asthma and COPD in addition to its earlier approval in rheumatoid arthritis.
- **ROCHE's Elecsys** Vitamin D assay, a fully automated vitamin D test for use on its cobas modular platforms, was cleared for use.
- **SIEMENS HEALTHCARE's Magnetom Spectra**, a 3-Tesla MRI system, received 510(k) clearance.

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European regulatory news

- **ABBOTT LABORATORIES' Humira (adalimumab)** – The EMA's Committee for Medicinal Products for Human Use (CHMP) recommended approval to treat moderate Crohn's disease.
- **ASTRAZENECA/MEDIMMUNE's FluMist/Fluenz** – The U.K. Department of Health is expanding its seasonal flu vaccination program to cover ***all*** children for free with this flu vaccine, making it the first nation to do that.
- **BOEHRINGER INGELHEIM and LILLY's Jentadueto (linagliptin + metformin)** was approved by the European Commission to treat Type 2 diabetes.
- **Calcitonin nasal spray** – The European Medicines Agency (EMA) recommended withdrawing this nasal spray used to treat osteoporosis because of an increased risk of cancer. The EMA also warned that long-term use of calcitonin-containing medicines given by injection or infusion also increases the risk for cancer, so they should be used only on a short-term basis for three conditions: Paget's disease, acute bone loss resulting from sudden immobilization, and hypercalcemia caused by cancer.
- **CELGENE's Istodax (romidepsin)** – CHMP recommended that this drug to treat peripheral T-cell lymphoma be rejected. Celgene reportedly plans to file a request for reconsideration of the decision.
- **CELLAEGIS DEVICES' autoRIC**, a portable device designed to automate the way doctors perform point-of-care remote ischemic conditioning (which is used to shield patients from ischemia-reperfusion injury during a heart attack), was granted a CE Mark.
- **FH ORTHOPEDICS' CP-ESP**, a cervical elastic spinal disc, received a CE Mark.

- **FOREST LABORATORIES and ALMIRALL's Tudorza Pressair (aclidinium bromide)** – a BID, inhaled, long-acting, muscarinic 3 receptor agonist – was approved to treat COPD.
- **GUIDED THERAPEUTICS' LuViva Advanced Cervical Scan** received a CE Mark.
- **INTELLIGENTMDX's HSV-1/2**, an automated assay to identify herpes simplex and to differentiate herpes 1 from herpes 2, was approved. It is used with **Abbott's m2000** assay.
- **JOHNSON & JOHNSON's Dacogen (decitabine)** – CHMP recommended approval for patients age ≥65 with newly diagnosed or secondary acute myeloid leukemia (AML) who are not eligible for standard chemotherapy. In March 2012, the FDA rejected this indication.
- **LAZARUS EFFECT's ReCover** ischemic stroke device for use during thrombectomy procedures received a CE Mark.
- **MERCK's Zostavax** – The U.K. plans to offer this shingles vaccine for free to everyone age ≥70 starting in 2013.
- **PFIZER:**
  - **bazedoxifene/conjugated estrogens** – The EMA is reviewing this drug to treat estrogen-deficiency symptoms and osteoporosis in postmenopausal women, with a decision expected in 2013.
  - **Xalkori (crizotinib)** – CHMP recommended approval to treat patients with ALK-positive advanced non-small cell lung cancer.
- **SUNSHINE HEART's C-Pulse** cardiac assist device, which is used to treat patients with Class III-IV heart failure, received a CE Mark.
- **TAKEDA's Adcetris (brentuximab vedotin)** – CHMP recommended approval to treat Hodgkin's lymphoma and systemic anaplastic large cell lymphoma.

The U.K.'s National Institute for Health and Clinical Excellence (NICE) news

BAYER's Xarelto (rivaroxaban) – NICE affirmed its recommendation that Xarelto be covered by the National Health Service (NHS) to treat pulmonary embolism and deep vein thrombosis.

Regulatory news from other countries

Brazil: **COVIDIEN's Solitaire FR** revascularization device, which is used to remove blood clots in acute ischemic stroke patients, was approved.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	July 2012	
July 30	**Regeneron's Arcalyst** (rilonacept) for gout	PDUFA date
July 30	**Almirall and Forest Laboratories' aclidinium** inhaled therapy for chronic obstructive pulmonary disease (COPD)	PDUFA date
	August 2012	
August 4	**Regeneron Pharmaceuticals** and **Sanofi's Zaltrap** (aflibercept) for colon cancer	PDUFA date
August 9	Draft guidance on **tablet scoring** and CDER's **nanotechnology** risk management working group activities	FDA's Pharmaceutical Science and Clinical Pharmacology Advisory Committee
August 10	**Roche/Genentech's Lucentis** (ranibizumab) to treat diabetic macular edema (DME)	PDUFA date
August 12	**Talon Therapeutics' Marqibo** (vincristine sulfate liposomes injection) for Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL)	PDUFA date (extended from May 13)
August 17	**Amarin's Vascepa** (icosapent ethyl, AMR-101), an FDA-approved omega-3 fatty acid for lowering high triglycerides	FDA decision expected on NCE status
August 21	**Pfizer's tofacitinib**, an oral JAK2 inhibitor for rheumatoid arthritis	PDUFA date
August 27	**Gilead Sciences' Quad** (emtricitabine+tenofovir+elvitegravir+cobicistat) for HIV	PDUFA date
	Other 2012	
September tba	**Vivus' Qnexa** (topiramate + phentermine) for obesity	EMA oral hearing
September 5	**Salix Pharmaceuticals' Provir** (crofelemer) for HIV-related diarrhea	PDUFA date (extended from June 5)
September 5	**Novartis' tobramycin inhalation powder** for management of cystic fibrosis patients infected with *Pseudomonas aeruginosa*	FDA's Anti-Infective Drugs Advisory Committee
September 8	**Ironwood Pharmaceuticals and Forest Laboratories' linaclotide** for irritable bowel syndrome	PDUFA date
September 10	**Navidea Biopharmaceuticals' Lymphoseek** (tilmanocept), a radioactive agent for tracing lymph nodes in cancer patients	PDUFA date (extended from June 10)
September 13	**Cornerstone Therapeutics/Cardiokine Biopharma's lixivaptan** for treatment of symptomatic hypervolemic and euvolemic hyponatremia associated with heart failure and syndrome of inappropriate antidiuretic hormone (SIADH) and **West-Ward Pharmaceutical's phenylephrine hydrochloride injection** to increase blood pressure in acute hypotensive states (e.g., shock and peri-operative hypotension)	FDA's Cardiovascular and Renal Drugs Advisory Committee
September 14	**Novartis' Gleevec** (imatinib) for adjunctive therapy of pulmonary arterial hypertension	FDA's Cardiovascular and Renal Drugs Advisory Committee
September 21	Classification of posterior **cervical screws**, including pedicle and lateral mass screws	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
September 23	**Regeneron's Eylea** (aflibercept) for central retinal vein occlusion (CRVO)	PDUFA date
September 27-28	Regulatory science considerations for performance validation of **radiation biodosimetry** devices	FDA public meeting
September 28	**Second Sight's Argus II Retinal Prosthesis System** for severe to profound retinitis pigmentosa	FDA's Ophthalmic Devices Advisory Committee
October 12	**Celgene's Abraxane** (nab-paclitaxel) to treat NSCLC	PDUFA date
October 21	**Impax Laboratories' IPX-066** for Parkinson's disease	PDUFA date
October 29	**Cornerstone Therapeutics' CRTX-080** to treat hyponatremia	PDUFA date
October 29-31	**Bayer's regorafenib** for metastatic CRC	PDUFA date
November 8	**Novo Nordisk's Tresiba** (degludec) **and Ryzodeg** (degludecPlus)	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
December 15	**Human Genome Sciences' raxibacumab** to treat anthrax	PDUFA date
December 21	**Alexa Pharmaceuticals' Adasuve** (loxapine) for agitation associated with schizophrenia or bipolar disorder	PDUFA date
December 28	**Biogen Idec's BG-12** for multiple sclerosis	PDUFA date

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	2013	
January 29	**Sanofi/Genzyme and Isis Pharmaceuticals' Kynamro** (mipromersen) for homozygous familial hypercholesterolemia	PDUFA date
January 30	**Raptor Pharmaceutical's cysteamine bitartrate** delayed-release (RP-103) to treat nephropathic cystinosis	PDUFA date
February 10	**Celgene's pomalidomide** for relapsed/refractory multiple myeloma	PDUFA date
February 24	**Dynavax's Heplisav** hepatitis B vaccine	PDUFA date
March 1	**Zogenix's Zohydro** (extended-release hydrocodone) for chronic pain	PDUFA date
April 11	**Sanofi/Genzyme and Bayer's Lemtrada** (alemtuzumab) for multiple sclerosis	PDUFA date