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
772-334-7409
Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

NOTE: ***Quick Takes*** will not publish December 23 or 30 but will resume (with three weeks of news) on January 6, 2013. Have a nice holiday.

SHORT TAKES

- **ABIOMED's Impella** – The company said the FDA will allow it to continue to sell this temporary percutaneous ventricular assist device until the company can submit – and receive approval through – a new premarket approval (PMA) application. The device was approved under the 510(k) pathway but has been reclassified as a Class III device, which requires a PMA submission.

- **ACTELION's Opsumit (macitentan)** – The company announced that the FDA accepted its new drug application (NDA) for this dual endothelin receptor antagonist to treat pulmonary arterial hypertension.

- **Alzheimer's disease** – A study reported in ***Nature Medicine*** suggested that beta-amyloid (Aβ) in the brain could be stopped by targeting a scaffolding protein, β-arrestin 2, which is elevated in the brains of Alzheimer's patients and interacts with gamma-secretase to increase Aβ production. Deleting β-arrestin 2 cut soluble Aβ in a mouse model of Alzheimer's without any obvious ill effects.

- **AMPHASTAR PHARMACEUTICALS' Primatene Mist** – The House of Representatives voted 229-182 against allowing this inhaled over-the-counter asthma medication – which contains epinephrine and uses the banned chlorofluorocarbon (CFC) as a propellant – to be marketed again so the company could sell the ~1.2 million inhalers still in stock.

- **ASTRAZENECA and RIGEL PHARMACEUTICALS' fostamatinib** – This investigational Syk inhibitor for rheumatoid arthritis showed no benefit over **Abbott's Humira** (adalimumab) in the 280-patient Phase IIb OSKIRA-4 trial. Fostamatinib was significantly better than placebo at 6 weeks (primary endpoint 1), but was inferior to Humira at Week 24 (primary endpoint 2).

- **Autism** – A study published in the journal ***Translational Psychiatry*** found that bumetanide, a loop diuretic, may improve some of the symptoms of autism, especially mild autism, such as eye contact, non-verbal communication, and social communication.

- **BAYER and ALGETA's Alpharadin (radium-223 dichloride)** was submitted to the European Medicines Agency to treat castration-resistant prostate cancer (CRPC) patients with bone metastases.

- **CUBIST PHARMACEUTICALS' CB-315 and CXA-201 (ceftolozane/tazobactam)** – The company said the FDA classified both of these Phase III investigational antibiotics

Qualified Infectious Disease Products (QIDP) – a new designation that is part of the Generating Antibiotic Incentives Now Act – and will be eligible for fast track status. CXA-201 is an IV treatment for complicated intra-abdominal infections and urinary tract infections, and CB-315 is an oral treatment for *Clostridium difficile*-associated diarrhea.

- **DURATA THERAPEUTICS' dalbavancin**, an investigational antibiotic for certain Gram-positive bacterial skin infections, met the primary endpoint in the Phase III DISCOVER-1 trial, stopping the spread of infection and reducing fever. Dalbavancin, given once a week for two weeks, was non-inferior to vancomycin BD given for 14 days. Development is being done under a Special Protocol Assessment (SPA) with the FDA, and the company plans to submit dalbavancin to the FDA in early 2013.

- **FUNCTIONAL NEUROMODULATION's DBS-fornix –** The company has started enrolling U.S. patients in ADVANCE, a 20-patient, double-blind trial of deep-brain stimulation of the fornix (DBS-f) as a treatment to improve memory in patients with mild Alzheimer's disease. So far, six institutions in North America are participating in the study, including Johns Hopkins and the University of Pennsylvania. The trial will compare the effects of DBS turned on to the effects of the device turned off. *If you believe this, there is a bridge in Brooklyn for sale.*

- **FZIOMED's Oxiplex Gel –** Four years after the FDA rejected this absorbable, clear, viscoelastic gel that some surgeons apply during lumbar spine surgery immediately prior to wound closure, FzioMed filed a petition for reconsideration with the FDA, charging that the product has proven itself in four studies with a total of >500 patients and with 10 years of commercial use on >300,000 patients outside the U.S. Oxiplex is available in ~70 countries – nearly everywhere except the U.S.

- **GILEAD SCIENCES** is buying **YM BioSciences**, which has an oral JAK2 inhibitor, CYT-387, in development to treat myelofibrosis. CYT-387 is expected to start Phase III trials in 2H13.

- **GW PHARMACEUTICALS' Sativex (delta-9-tetrahydro-cannabinol & cannabidiol) –** A report in the ***Drug and Therapeutics Bulletin*** said there is "meager" evidence that the use of this cannabis extract spray is effective in treating muscle spasms in multiple sclerosis patients and that its routine use can't be justified. The report cited flaws in the clinical trials of Sativex, including short duration, small number of patients, and dosing issues. The company called the journal report misleading and said it contained a number of errors.

- **HIV –** In a study reported in the journal ***PLoS ONE***, researchers at the University of Washington developed nanometer-sized fibers that can be electrically spun into a mesh cloth that has a medical use. The cloth (made out of glycerol monolaurate, a common food/cosmetic additive) can be embedded with a drug, the cloth quickly dissolves, and the drug is then released. Potential uses include diaphragms, cervical caps, and vaginal films for both contraception and HIV prevention.

- **JOHNSON & JOHNSON's canagliflozin + metformin –** The company submitted an NDA for a fixed-dose combination of these two drugs to treat Type 2 diabetes.

- **LUNDBECK and TAKEDA's Brintellix (vortioxetine) –** The company said the FDA accepted its NDA filing for this antidepressant to treat major depressive disorder in adult patients.

- **Melanoma –** In a paper in ***Cancer Discovery***, a journal of the American Association for Cancer Research (AACR), Yale researchers reported that combining a statin with a cyclin-dependent kinase (CDK) inhibitor may be effective in treating refractory melanomas driven by mutations in the NRAS and KRAS genes. RAS mutations occur in ~20% of melanomas. In this study, the combination was simvastatin + flavopiridol. *Watch for studies of various statins with CDK inhibitors.*

- **MILO BIOTECHNOLOGY's AAV1-FS344**, an investigational treatment for Becker and Duchenne muscular dystrophy, was granted orphan drug status.

- **Naltrexone –** A 700-patient study, published in the journal ***Biological Psychiatry***, found this opioid blocker did ***not*** help women quit smoking any better than placebo, but the women who did quit gained "far less" weight over three months than placebo patients (2.3 pounds vs. 5.1 pounds). The drug did help men quit smoking.

- **NPS PHARMACEUTICALS' Gattex (teduglutide, U.S.) and TAKEDA/NYCOMED's Revestive, Europe) –** A Phase III study published in the journal ***Gastroenterology*** found that this GLP-2 analog reduced the need for parenteral support in patients with short bowel syndrome (SBS) with intestinal failure, with 63% of teduglutide patients vs. 30% of placebo patients responding ($p=0.002$). At Week 24, the average reduction in parenteral support volume was 4.4 L/week for teduglutide patients vs. 2.3 L/week for placebo ($p<0.001$).

- **PORTOLA PHARMACEUTICALS' PRT-4445 –** A Phase II trial of this potential "universal antidote" for oral Factor Xa inhibitors has started.

- **ROCHE/GENENTECH's Avastin (bevacizumab)** – A 2,673-patient study published in the ***Journal of Clinical Oncology*** found that adding Avastin to standard chemotherapy for Stage II or III colorectal cancer (CRC) did not extend survival. Last month, the AVANT trial found Avastin did not improve disease-free survival in resected Stage III or high-risk Stage II CRC and, in fact, Avastin patients had more relapses and deaths due to progression. *Is there anyone who still believes Avastin is useful in adjuvant CRC?*

- **SANOFI's Lovenox (enoxaparin)** – A study published in the ***Archives of Internal Medicine*** found that this low molecular weight heparin was associated with an increased risk of major bleeding in patients with moderate renal impairment vs. patients with normal renal impairment (22.0% vs. 5.7%), with an odds ratio of 3.9.

- **TOKAI PHARMACEUTICALS' galeterone (TOK-001)** – The company started a 196-patient Phase II trial of this oral androgen receptor antagonist for CRPC.

NEWS IN BRIEF

Alternative medicine – getting new attention from pharmas

At least three major pharmas are looking at Chinese herbal remedies to see if the plant-based therapies can be turned into botanical treatments, a less cumbersome FDA approval pathway. For instance:

- **GlaxoSmithKline** is testing plant extractions to treat immune disorders.

- **Sanofi** is investigating traditional Chinese medicines to treat diabetes and cancer.

- **Nestle** plans to develop a drug derived from ancient Chinese approaches for treating inflammatory bowel disease.

ASTRAZENECA

- **Antisense drugs.** AstraZeneca and **Isis Pharmaceuticals** formed a strategic alliance to develop novel antisense drugs against five targets in oncology. Under the agreement, AstraZeneca gets the rights to Isis' STAT3Rx, an investigational therapy for advanced lymphomas that is in Phase I development.

- **AZD-5847.** A Phase IIa trial of this investigational antibiotic (for Gram-positive bacteria) to treat tuberculosis started in South Africa.

CELGENE

- **Revlimid (lenalidomide).** A 15-patient study published in ***Arthritis Research & Therapy*** found that this oral multiple myeloma drug was effective and safe in treating refractory cutaneous lupus erythematosus (CLE). At 15 months, 86% showed a complete response. However, three-quarters of patients relapsed when the drug was withdrawn.

- **Vidaza (azacitidine)** – A 53-patient Phase II trial reported at the American Society of Hematology meeting found that an oral formulation – 300 mg/day administered for ≤21 days per 4-week cycle – was safe and effective in patients with lower-risk myelodysplastic syndrome (MDS). Currently, Vidaza is administered IV. A Phase III trial of the oral formulation is now underway.

LILLY

- **Solanezumab.** After meeting with the FDA, Lilly said it is ***not*** going to submit a Biologics License Application (BLA) for this IV treatment for Alzheimer's disease (AD) to the FDA – yet. Instead, it is going to do another study to confirm the efficacy of the anti-beta amyloid monoclonal antibody, and that study is not expected to be finished until 2H15, with no launch (if approved) probably until 2017. While the two completed Phase III trials missed their primary endpoints, a pooled analysis indicated an improvement in cognition, particularly in mild AD patients, though not function. Experts had expected (and wanted) Lilly to submit the data anyway. *Obviously, the FDA dashed any hopes of approval on those data. Is Lilly putting good money after bad?*

- **Tabalumab (LY-2127399).** The company halted the FLEX-M trial (one of three Phase III trials) of this investigational BAFF inhibitor for moderate-to-severe rheumatoid arthritis (RA) after a planned interim analysis found the efficacy goal was futile. The other 2 RA Phase III trials (in different patient populations) are continuing, but no new patients are being enrolled until additional analyses of those trials are completed in early 2013.

Spinal fusion

- Safety questioned by AHRQ. The U.S. Agency for Healthcare Research and Quality (AHRQ), whose reports are often used by commercial payors in determining coverage policies, announced that it is conducting a comparative effectiveness review of the safety and effectiveness of spinal fusion for lumbar back pain. AHRQ reports are often used by commercial payors to help set coverage policies. AHRQ said there is "limited evidence" that spinal fusion is more effective than physical therapy and that there is insufficient

reporting of adverse events. Public comments are being accepted until December 18, 2012.

- **New spine organization.** The Society for Advanced Spinal Intervention (SASI) was founded by an interventional pain physician to provide training and education to physicians in the field of spine care, including interventional pain physicians, interventional radiologists, neurosurgeons, and orthopedic spine surgeons. SASI plans to establish a U.S.-based training and credentialing program for doctors from around the world.

REGULATORY NEWS

FDA wants input on new trial rules

The FDA issued draft guidance designed to help institutional review boards, clinical trial sponsors, and researchers set investigator qualifications, decide whether research sites are adequate, and determine whether an investigational new drug application (IND) or investigational device exemption (IDE) is necessary to protect human subjects. The Agency is accepting public comment through January 22, 2013.

MedPAC tells Congress to repeal SGR

The Medicare Payment Advisory Commission (MedPAC) gave Congress the same advice as last year: Repeal the sustainable growth rate (SGR) formula that sets payment for doctors under Medicare and replace it with 10 years of statutory payment updates. MedPAC also recommended:

- That Congress rebalance payment across specialties by freezing primary care payments and reducing all other specialties, so primary care providers get on an equal footing with specialists.
- Collecting data to improve payment accuracy and to identify overpriced services.
- Incentivizing the growth of accountable care organizations (ACOs) by raising the amount of money plans can get under "shared savings" programs.
- Raise out-of-pocket costs for beneficiaries.
- Reduce payments to hospitals and home health services.

FDA approvals/clearances

- **ARIAD PHARMACEUTICALS' Iclusig (ponatinib)**, a third-generation tyrosine kinase inhibitor (a pan-BCR-ABL inhibitor), was approved to treat chronic myeloid leukemia (CML) and Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). The approval came 3 months before the PDUFA date.
- **BLUE BELT TECHNOLOGIES' NavioPFS**, a robot-assisted system for partial knee replacement procedures, was cleared for use.
- **BRISTOL-MYERS SQUIBB's Baraclude (entecavir)** – The FDA approved new labeling that adds information for treating black patients with hepatitis B virus (HBV) as well as recipients of liver transplants who have the disease.
- **GLAXOSMITHKLINE's ABthrax (raxibacumab)** was approved to treat inhalation anthrax. It is the first monoclonal antibody to be approved under the FDA's Animal Efficacy Rule, which allows efficacy findings from adequate and well-controlled animal studies to support approval when it is not feasible or ethical to conduct trials in humans.
- **JOHNSON & JOHNSON's Zytiga (abiraterone)** received expanded approval for use with prednisone before chemotherapy in men with metastatic CRPC. In 2011, it was approved for use after docetaxel.
- **LENSAR's LensAR Laser System** received expanded approval for use in performing corneal incision in cataract patients.
- **MERIT MEDICAL SYSTEMS' ONE Snare**, a single-loop snare used to manipulate and retrieve foreign objects during endovascular procedures, received 510(k) clearance.
- **SUCAMPO PHARMACEUTICALS' Rescula (unoprostone isopropyl 0.15%)** was approved to lower intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma. The company plans to launch the drug in 1Q13.

FDA recalls/warnings

- **HOSPIRA's carboplatin** – The company issued a voluntary nationwide recall of three lots of this chemotherapy drug after a routine sample inspection found visible particles that were identified as carboplatin crystals.
- **Judge Rotenberg Educational Center** in Canton MA received a warning letter saying that the Graduated Electronic Decelerators (GEDs) it uses to shock patients with autism and severe behavioral disabilities are in violation of FDA regulations and that an application for approval must be submitted.

- **MEDART** received an FDA warning letter that the medical lasers it manufactures in Denmark are misbranded. The letter cited Form 483 deficiencies, including failure to adequately develop, maintain, and implement written medical device reporting (MDR) procedures as well as violations of current good manufacturing practice (cGMP) requirements.
- **PFIZER's Chantix (varenicline)** – The FDA issued an updated Safety Communication saying that a large meta-analysis performed at the FDA's request still can't answer the question of whether the excess risk of major cardiovascular adverse events (MACE) with this stop-smoking medication is due to the drug or to chance. MACE was uncommon in both the Chantix and placebo groups, and the increased risk was not statistically significant.

  As a result, the FDA updated the Chantix label with the trial results, advised healthcare professionals to weigh the risks and benefits in individual patients, and urged patients to contact their doctors if they experience worsening symptoms of cardiovascular disease.
- **QUALITEST's hydrocodone bitartrate and acetaminophen 10 mg/500 mg tablets** – The company recalled 101 lots because they may contain excess levels of acetaminophen.
- **RTI BIOLOGICS** got a warning letter from the FDA after investigators found significant deviations from regulations for human cells, tissues, and cellular and tissue-based products. Among the problems were contamination of human body parts and bone putty with *Pseudomonas* and other pathogens on numerous occasions. Despite the company's corrective actions, the FDA remains concerned about "ongoing contamination issues that appear to be problematic throughout [the] facility."

European regulatory news

- **BOSTON SCIENTIFIC's Precision Spectra**, an implantable spinal stimulation device, was approved to treat chronic pain.
- **CYTOMEDIX's Angel**, a concentrated platelet-rich plasma technology with bone marrow aspirate, received a CE Mark.
- **LIFEWATCH's LifeWatch V**, a smartphone device for wirelessly monitoring blood glucose levels, heart rate, and other health information, received a CE Mark.
- **MAUNA KEA TECHNOLOGIES' Cellvizio UroFlex**, an optical biopsy probe, received a CE Mark for use in urology (bladder cancer) as well as lung and gastrointestinal biopsies.
- **NEXSTIM OY's Navigated Brain Therapy System**, which uses MRI-enabled navigation to administer transcranial magnetic stimulation therapy to targeted areas of the brain to treat acute depression or help patients recover after a stroke, received a CE Mark.
- **ROCHE's Perjeta (pertuzumab)** – The European Medicine Agency's Committee for Medicinal Products for Human Use (CHMP) recommended approval of this monoclonal antibody for use in combination with Roche's **Herceptin** (trastuzumab) and docetaxel in patients with HER2-positive metastatic or locally recurrent unresectable breast cancer.
- **SANOFI/GENZYME's Thyrogen (thyrotropin alfa)** received expanded approval for use with a wider irradiation dose range for postoperative thyroid remnant ablation.

Regulatory news from other countries

- ***Canada:***
  - **Advertising.** The Pharmaceutical Advertising Advisory Board, which approves drug advertising, amended parts of its Code of Advertising Acceptance to allow Internet and social media advertisers to include a URL or link to the terms of market authorization approved by Health Canada for the drug rather than attach a copy. The new rules will be enforced starting July 1, 2013.
  - **BRISTOL-MYERS SQUIBB and PFIZER's Eliquis (apixaban)** was approved for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AFib). It was already approved in Canada for the prevention of venous thromboembolic events (VTE) in patients undergoing knee/hip replacement surgery.
  - **COVIDIEN's Solitaire FR** revascularization device for blood clot removal and blood flow restoration in the brains of acute ischemic stroke patients was approved for use by Health Canada.
- ***Japan:*** **THORATEC's HeartMate II** left ventricular assist device was approved for bridge-to-transplant. It will be distributed by **Nipro** in Japan, with the commercial launch to start after reimbursement is in place and sites are trained, which is likely to mean the end of 1Q13.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	2012	
December 17	**Amarin's Vascepa** (icosapent ethyl, AMR-101), an omega-3 fatty acid pill	FDA NCE decision expected *(extended from November 16, 2012)*
December 20	**Hemispherx Biopharma's Ampligen** (rintatolimod injection, poly I: poly C12U) to treat chronic fatigue syndrome (CFS)	FDA's Arthritis Advisory Committee
December 21	**Alexza Pharmaceuticals' Adasuve** (loxapine) for agitation associated with schizophrenia or bipolar disorder	PDUFA date
December 29	**Aegerion Pharmaceuticals' lomitapide** to treat homozygous familial hypercholesterolemia	PDUFA date
December 29	**Johnson & Johnson's Sirturo** (bedaquiline) to treat multi-drug resistant tuberculosis	PDUFA date
December 30	**NPS Pharmaceuticals' Gattex** (teduglutide) for short bowel syndrome	PDUFA date
	2013	
January 10	**Johnson & Johnson's Invocana** (canagliflozin), an SGLT2 inhibitor to treat Type 2 diabetes	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
January 16	**Santarus' Uceris** (budesonide) for ulcerative colitis	PDUFA date (extended from October 16, 2012)
January 17	**NuPathe's Zelrix** (transdermal sumatriptan), a migraine patch	PDUFA date
January 21	**Impax Laboratories' Rytary** (IPX-066) for Parkinson's disease	PDUFA date (extended from October 21, 2012)
January 29	**Boehringer Ingelheim's Striverdi Respimat** (olodaterol) for chronic obstructive pulmonary disease (COPD)	FDA's Pulmonary-Allergy Drugs Advisory Committee
January 29	**Sanofi/Genzyme** and **Isis Pharmaceuticals' Kynamro** (mipomersen) for homozygous familial hypercholesterolemia	PDUFA date
January 30	**Pharmaxis' Bronchitol** (mannitol inhalation powder) for the management of cystic fibrosis	FDA's Pulmonary-Allergy Drugs Advisory Committee
January 30	**Raptor Pharmaceutical's cysteamine bitartrate** delayed-release (RP-103) to treat nephropathic cystinosis	PDUFA date
February 2	**Hemispherx Biopharma's Ampligen** (rintatolimod injection, poly I: poly C12U) to treat chronic fatigue syndrome	PDUFA date
February 10	**Celgene's pomalidomide** for relapsed/refractory multiple myeloma	PDUFA date
February 22	**NeuroPace's RNS system,** a neuromodulation system for epilepsy	FDA's Neurological Devices Advisory Committee
February 24	**Dynavax's Heplisav** hepatitis B vaccine	PDUFA date
February 26	**Roche/Genentech** and **ImmunoGen's trastuzumab emtansine** (T-DM1) to treat unresectable locally advanced or metastatic HER2+ breast cancer	PDUFA date
February 28	**Lundbeck** and **Otsuka's aripiprazole depot** to treat schizophrenia	PDUFA date
March tba	**Johnson & Johnson's Invocana** (canagliflozin), a SGLT2 inhibitor to treat Type 2 diabetes	PDUFA date
March 1	**Zogenix's Zohydro** (extended-release hydrocodone) for chronic pain	PDUFA date
March 17	**Bristol-Myers Squibb** and **Pfizer's Eliquis** (apixaban,) an oral anticoagulant to prevent stroke in atrial fibrillation patients	PDUFA date
March 28	**Biogen Idec's BG-12** (dimethyl fumarate) for multiple sclerosis	PDUFA date (extended from December 28, 2012)
April 29	**Shire's Vyvanse** (lisdexamfetamine dimesylate), sNDA for ADHD treatment in children	PDUFA date
May 12	**GlaxoSmithKline** and **Theravance's Breo/Relvar** (fluticasone furoate + vilanterol) to treat chronic obstructive pulmonary disease (COPD)	PDUFA date
May 31	**DepoMed's Serada** (gabapentin extended-release), a hot-flash treatment	PDUFA date
June 20	**Dainippon Sumitomo Pharma/Sunovion Pharmaceuticals' Latuda** (lurasidone), a schizophrenia drug for use in treating bipolar disorder	PDUFA date
July 28	**Aveo Oncology** and **Astellas Pharma's Tivopath** (tivozanib) to treat advanced renal cell carcinoma	PDUFA date
October 2	**Lundbeck** and **Takeda's Brintellix** (vortioxetine), an antidepressant for major depressive disorder	PDUFA date
October 19	**Actelion's Opsumit** (macitentan), a dual endothelin receptor antagonist to treat pulmonary arterial hypertension	PDUFA date