TRENDS-in-MEDICINE

September 9, 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…

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: Subscribe to ***Trends-in-Medicine*** for coverage of the **European Federation of Neurological Societies** meeting in Stockholm, Sweden.

SHORT TAKES

- **ASCENSION** is acquiring **Marian Health System**.
- **Barrett's esophagus –** A U.K. study published in ***Nature Genetics*** reported on the first genetic variations – SNPs on 6p21 and 16q24 – linked to the onset of this pre-cancerous condition, which could lead to a screening test.
- **CELGENE's apremilast –** The company said this investigational PDE-4 inhibitor met the primary endpoint in two Phase III trials in psoriatic arthritis. Celgene plans to submit apremilast to the FDA in 1Q13.
- **CHINA SKY ONE MEDICAL** and its top executives were sued by the U.S. Securities and Exchange Commission (SEC), which claims they inflated revenue with fake sales of a diet product, a "slim patch."
- **CONVATEC** is buying **180 Medical Holdings**, a catheter and urologic medical supply company.
- **IVIG –** A study published in the ***New England Journal of Medicine*** found that even small doses of intravenous immunoglobulin (IVIG) can cause acute, severe (hemolytic) anemia. Sofya Pintova, MD, of Mount Sinai School of Medicine and colleagues reported on two cases that occurred in Guillain-Barré syndrome patients after a total dose of only 125 g to 225 g of IVIG, and they warned other doctors to be cautious.
- **JOHNSON & JOHNSON's bedaquiline –** The FDA granted priority review for this investigational treatment for multidrug-resistant tuberculosis.
- **KV PHARMACEUTICAL's Makena (hydroxyprogesterone caproate injection) –** A U.S. district judge dismissed the company's lawsuit against the FDA, saying she would not interfere with the FDA's enforcement activities.
- **LILLY's Alimta (pemetrexed) –** This chemotherapy regimen failed to extend overall survival when added to **Roche/Genentech's Avastin** (bevacizumab) in patients with non-squamous non-small cell lung cancer.
- **MERGE HEALTHCARE –** This healthcare information technology company is exploring selling itself after getting a letter from the FDA last month saying its response was inadequate to violations found during a manufacturing inspection of its blood-pressure computer kiosks.

- **NOVARTIS' TIP (tobramycin inhalation powder)** – The FDA's Anti-Infective Drugs Advisory Committee voted 13-1 that the company presented "adequate evidence" of safety and efficacy for this inhaled dry-powder form of an antibiotic often used by patients with cystic fibrosis.

- **NPS PHARMACEUTICALS' Natpara [recombinant human parathyroid hormone, rhPTH (1-84)]** – The company said the FDA has requested revisions to the instructions for use of the injection pen that will deliver this investigational treatment for adult hypoparathyroidism, and that will delay filing of the biologics license application (BLA) until mid-2013. However, the company said the FDA is not asking for additional clinical data.

- **PFIZER's Aricept (donepezil)** – Public Citizen sued the FDA, seeking a federal court order that would force the FDA to make a decision within 30 days on the Citizen Petition that Public Citizen filed in May 2011 demanding removal of the higher (23 mg) dose of Aricept, which it claims has not shown any clinically meaningful benefit but significantly increases potentially life-threatening side effects.

- **PLURISTEM THERAPEUTICS' PLacental eXpanded cells** – The company submitted an orphan drug application to the FDA for aplastic anemia. The therapy already has orphan drug status for Buerger's disease.

- **Prostate cancer** – A study published in the ***New England Journal of Medicine*** found that intermittent androgen-deprivation therapy is as effective as continuous therapy in treating men with localized prostate cancer. There was no statistically significant difference in overall survival (8.8 years with intermittent therapy and 9.1 years with continuous therapy) or 7-year disease-related mortality (18% vs. 15%). However, there were benefits in terms of functional, symptomatic, and sexual response with intermittent therapy.

- **QUESTCOR PHARMACEUTICALS' Acthar Gel (adreno-corticotropic hormone, ACTH)** – The Centers for Medicare & Medicaid Services (CMS) said the company can provide significantly lower Medicaid rebates on this drug to treat exacerbations in multiple sclerosis patients (as well as other conditions), which should help improve the company's bottom line. *The issue still is convincing doctors to prescribe it, given the very high cost.*

- **SALIX PHARMACEUTICALS' Provir (crofelemer)** – For the second time, the FDA said it needed more time to make a decision on the approval of a 125-milligram dose of this treatment for HIV-related diarrhea. The original PDUFA date was June 5, which was postponed to September 5. A new PDUFA date was not announced.

- **SPECTRUM PHARMACEUTICALS** – The Federal Trade Commission approved Spectrum's acquisition of **Allos Therapeutics**.

- **VALEANT PHARMACEUTICALS** is buying **Medicis Pharmaceutical**. *At the American Academy of Dermatology (AAD) meeting in March 2012, Valeant officials said the company was in acquisition mode in aesthetics, so this shouldn't come as a big surprise.*

NEWS IN BRIEF

BOEHRINGER INGELHEIM's Pradaxa (dabigatran) – on- and off-label use increasing

A study by researchers at Johns Hopkins Bloomberg School of Public Health, published in ***Circulation: Cardiovascular Quality and Outcomes***, found increasing off-label use of this oral anticoagulant beyond the approved indication of stroke reduction in atrial fibrillation to include venous thromboembolism (VTE) prevention and coronary artery disease. At the end of 2011, Pradaxa had captured 18.9% of the anticoagulant market. Cardiologists accounted for 53% of Pradaxa prescriptions, internal medicine 28%, and primary care 10%.

Mammography – risky for young women at high risk of breast cancer

A study published in the ***British Medical Journal*** found that women with a high familial risk for breast cancer may ***increase*** their breast cancer risk if they have chest radiation (including a mammogram) before age 30. A retrospective analysis by Dutch researchers of 1,993 women with either a BRAC1 or BRAC2 mutation found that ***any*** diagnostic use of radiation before age 30 increased breast cancer risk by 90% – and mammography before age 30 increased the risk by 43% – for women with the mutation. Even one mammogram before age 30 increased the number of women developing breast cancer by age 40 from 9 to 14 out of 100.

CT exposure before age 30 also seemed to be associated with an increased risk of breast cancer (HR 2.36), but the confidence intervals were wide because the numbers were small. The researchers concluded that younger women should have other imaging done, such as an MRI.

Stem cells – may help in brain injury

A study by researchers at the Institute for Regenerative Medicine at Texas A&M Health Science Center, Duke University Medical Center, and the Veterans Affairs Medical Centers in Temple TX and Durham NC – funded by the National Institute of Neurological Disorders and Stroke and the Department of Veterans Affairs and published in ***STEM CELLS Translational Medicine*** – found that grafting neural stem cells from one part of the brain (the subventricular zone) into another (the hippocampus) restored cognition in brain-injured rats. Mood, memory, and mobility significantly improved in the rats that received the stem cells. The research also suggests that a neural stem cell transplant may be suitable for treating some neurodegenerative disorders.

Thyroid cancer – more accurate diagnostic assay developed

Italian researchers reported in ***BMC Cancer*** on new genetic tests they have developed that boost the accuracy of thyroid cancer detection while reducing unnecessary diagnostic thyroidectomies by nearly 50%. Using fine-needle aspiration to obtain tumor cell samples, investigators at the University of Pisa developed an 8-gene assay that measures gene expression more accurately than has been possible up to now, with 89% accuracy.

Ventricular assist devices (VADs) – CMS panel to review in November

CMS is convening a meeting of its Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) on November 14, 2012, to consider VADs, which currently are covered for three indications: postcardiotomy (after open-heart surgery); bridge-to-transplant (BTT), and destination therapy (DT) – each based on specific criteria. Currently, the devices are covered only when implanted in facilities and by operators meeting specific criteria.

It is not entirely clear why CMS is convening this MEDCAC, but CMS said it is seeking the panel's input on "whether or not the published evidence identifies facility and/or operator characteristics that predict clinically meaningful improvements" in patient outcomes. *Could CMS be considering expanding or limiting the number/type of centers approved to implant VADs?*

The voting questions are, as usual for MEDCAC, rather convoluted, but they basically are asking:

1. Are there criteria to identify patients who will benefit more from a VAD than from optimal medical therapy alone, and if so, what are those criteria? Are those criteria different for BTT and DT?
2. Are there facility/physician criteria that predict successful VAD outcomes, and if so, what are those criteria? In addition, how important is VAD certification, and what is the role of the "heart team" concept to patient management?
3. Which of these conclusions are generalizable to Medicare beneficiaries?
4. Are there clinically significant gaps remaining in the evidence about use of VADs?

REGULATORY NEWS

Counterfeit drug efforts

The FDA and China's State Food and Drug Administration shut down 18 Chinese-language websites offering counterfeit drugs in the U.S. Some of the sites offered erectile-dysfunction drugs without prescriptions, and others advertised a date-rape drug.

FDA reorganizing CDER

Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research (CDER), announced several changes within CDER, including:

- Elevating the Office of Generic Drugs (OGD) to a "super office" (with subordinate offices within it) that would report directly to Dr. Woodcock. This would put generic drugs on a par with the Office of New Drugs and the Office of Surveillance and Epidemiology, etc.
- Creating a new Office of Pharmaceutical Quality (OPQ) charged with oversight of quality throughout the life cycle of a drug. OPQ would take on some of the functions currently handled by the Office of Pharmaceutical Science (OPS) as well as other quality-related functions. Some functions of the Office of Manufacturing and Product Quality (OMPQ) in the Office of Compliance would be moved to the new OPQ, but other OMPQ enforcement and compliance functions would remain in the Office of Compliance.

ICD-10 a looming problem for doctors

A survey by **Nuesoft Technologies** found that medical practices across the country are worried about their transition to the ICD-10 coding system, even though the Department of Health and Human Services (HHS) postponed the start date to October 1, 2014. Seventy-three percent of practices said ICD-10 will significantly affect their practices, either financially or operationally.

IOM report on healthcare: improve waste-cutting

The Institute of Medicine (IOM) issued a 382-page report, *Best Care at Lower Cost: The Path to Continuously Learning Health Care in America*, that lays out a roadmap – a set of improvement strategies – that panel members believe will make healthcare information more accessible, engage patients and their families, and make care more equitable, and information technology plays a big role in those recommendations.

According to the IOM, the U.S. health system wastes $750 billion each year (~30% of every medical dollar), and the IOM suggests there are ways to make deep cuts in healthcare spending without rationing care. The key areas with waste are:

- Unnecessary services ($210 billion/year).
- Inefficient delivery of care ($130 billion/year).
- Excess administrative costs ($190 billion/year).
- Inflated prices ($105 billion/year).
- Prevention failures ($55 billion/year).
- Fraud ($75 billion/year).

Recommendations include full adoption of electronic medical records (EMRs), faster drug approvals, better physician training, and more even healthcare quality across the country. The report said, "The traditional systems for transmitting new knowledge – the ways clinicians are educated, deployed, rewarded, and updated – can no longer keep pace with scientific advances."

FDA approvals/clearances

- **AAP IMPLANTATE's Loqteq** plating system for orthopedic trauma patients was given 510(k) clearance.
- **FLEXICATH's M/29 Midterm** pressure-injectable catheter insertion devices, designed to help control bloodstream infections, were granted 510(k) clearance.
- **LDR HOLDING's Avenue L** lateral lumbar cage system was cleared for use in intervertebral body fusion of the lumbar spine.
- **OPTIMEDICA's Catalys Precision Laser System** received 510(k) clearance for use to help surgeons make multi-plane and single-plane incisions in the cornea during cataract surgery.
- **PFIZER's Bosulif (bosutinib)**, a tyrosine kinase inhibitor, was approved to treat chronic, accelerated, or blast phase Philadelphia-positive chronic myelogenous leukemia (CML).
- **ROCHE DIAGNOSTICS' herpes virus assays** – The FDA approved two automated assays for the IgG Antibody, which is used to spot herpes simplex virus types 1 and 2. The tests will run on the company's cobas modular analytical platforms.
- **SIEMENS' Multix Fusion**, a digital radiography tool, received 510(k) clearance.
- **STRIDES ARCOLAB/ONCO THERAPIES' injectable vinorelbine**, which is licensed to **Pfizer**, was approved to treat cancer.

FDA recalls/warnings

- **BAXTER's Automix intravenous feeding devices** – The FDA classified the recall of these devices, which was due to concerns that fluids could cause an electronic failure leading to the delivery of incorrect doses, as a Class I recall.
- **SUN PHARMACEUTICAL INDUSTRIES/CARACO PHARMACEUTICAL LABORATORIES' nimodipine capsules 30 mg** – One lot was voluntarily recalled "as a precautionary measure," due to the presence of crystals of nimodipine within the capsule solution, after a customer complaint.

European Union (EU) regulatory news

- **AMAG PHARMACEUTICALS' Rienso (ferumoxytol)** – which is approved in the U.S. and Canada as **Feraheme** – was approved in Switzerland to treat iron-deficiency anemia in adults with chronic kidney disease. It also has EU approval. **Takeda** will market it there.
- **CIRCULITE's Synergy**, a mini blood pump system, was granted a CE Mark.
- **HPV** – The European Centre for Disease Prevention and Control recommended ***all*** girls get the human papillomavirus vaccine. Current vaccination rates are very low, and the Agency would like to see more girls vaccinated.
- **JOHNSON & JOHNSON/JANSSEN-CILAG's oral bedaquiline (TMC-207)** was submitted to the European Medicines Agency (EMA) as part of combination treatment for multidrug-resistant tuberculosis.
- **NOVARTIS' Lucentis (ranibizumab)** – Novartis (which sells this VEGF inhibitor in Europe) said that long-term data showing both safety and efficacy in treating choroidal neovascularization (CNV) secondary to pathological myopia were positive, and it plans to submit Lucentis to the EMA in 3Q12 and in Japan by the end of 2012 for this indication.
- **PFIZER's Inlyta (axitinib)** was approved to treat advanced renal cell carcinoma.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	2012	
September tba	**Vivus' Qnexa** (topiramate + phentermine) for obesity	EMA oral hearing
September 10	**Postmarket monitoring** of medical devices	FDA public workshop
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 **WestWard Pharmaceutical's phenylephrine hydrochloride injection** to increase blood pressure in acute hypotensive states	FDA's Cardiovascular and Renal Drugs Advisory Committee
September 21	Classification of posterior **cervical screws**, including pedicle 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 3	Discussion of establishment of a new subcommittee to evaluate the FDA's efforts to address the **challenges in the Science Board's 2007 report**	FDA's Science Board
October 12	**Celgene's Abraxane** (nab-paclitaxel) to treat NSCLC	PDUFA date
October 15	Need for and design of **clinical development programs** for approval of **parenteral lipid emulsion products** as nutritional support	FDA's Gastrointestinal Drugs Advisory Committee
October 16	**NPS Pharmaceuticals' Gattex** (teduglutide) for short bowel syndrome	FDA's Gastrointestinal Drugs Advisory Committee
October 17	**Aegerion Pharmaceuticals' lomitapide** to treat homozygous familial hypercholesterolemia	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
October 17	**ThromboGenics' ocriplasmin** to treat vitreomacular adhesions	PDUFA date
October 18	**Sanofi/Genzyme** and **Isis Pharmaceuticals' Kynamro** (mipomersen) to reduce cholesterol in patients with homozygous familial hypercholesterolemia	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
October 21	**Impax Laboratories' IPX-066** for Parkinson's disease	PDUFA date
October 24	**Hologic's Selenia Dimensions 3D System –** expanded indication to combine digital breast tomosynthesis with synthetic 2D images for cancer screening	FDA's Radiological Devices Advisory Committee
October 29	**Cornerstone Therapeutics' CRTX-080** to treat hyponatremia	PDUFA date
October 29-30	Discussion of benefits, risks, and abuse of drugs containing **hydrocodone**	FDA's Drug Safety and Risk Management Advisory Committee
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
November 8-9	**Exelixis' cabozantinib** for progressive, unresectable, locally advanced or metastatic medullary thyroid cancer	FDA's Oncologic Drugs Advisory Committee (ODAC) – ***canceled***
November 9	**MSD Consumer Care's "Oxytrol for Women,"** an over-the-counter transdermal oxybutynin to treat overactive bladder in women	FDA's Non-prescription Drugs Advisory Committee
November 14	Optimization of outcomes with **ventricular assist devices** (VADs) for patients with heart failure	CMS' MEDCAC
November 22	**Medivation** and **Astellas' enzalutamide** (MDV-3100) for castration-resistant prostate cancer	PDUFA date
November 21	**Pfizer's tofacitinib**, an oral JAK inhibitor for rheumatoid arthritis	PDUFA date (extended from August 21)
November 28	Discussion of the use of **absorbable material** in a variety of medical devices	FDA Workshop on Absorbable Medical Devices: Lessons Learned From Correlations of Bench Testing and Clinical Performance
November 29	**Exelixis' cabozantinib** to treat medullary thyroid cancer	PDUFA date
December 15	**Human Genome Sciences' raxibacumab** to treat anthrax	PDUFA date
December 21	**Alexza 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
December 29	**Aegerion Pharmaceuticals' lomitapide** to treat homozygous familial hypercholesterolemia	PDUFA date
December 29	**Johnson & Johnson's bedaquiline** to treat multidrug-resistant tuberculosis	PDUFA date
December 30	**NPS Pharmaceuticals' Gattex** (teduglutide) for short bowel disease	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 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 29	**Sanofi/Genzyme** and **Isis Pharmaceuticals' Kynamro** (mipomersen) 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 – delayed because FDA rejected the filing