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…

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NOTE: Subscribe to ***Trends-in-Medicine*** for coverage of the **American Academy of Ophthalmology** meeting in Chicago, the **American Association for the Study of Liver Diseases** meeting in Boston, and the **American College of Rheumatology** meeting in Washington DC.

SHORT TAKES

- **AMGEN's Epogen (epoetin alfa) –** A Phase I trial found that giving EPO to neonates with hypoxic-ischemic encephalopathy (HIE) along with hypothermia treatment was well tolerated and may be neuroprotective.
- **ARSEUS** is acquiring drug compounding companies in Brazil, Colombia, and Scandinavia, and it plans several similar acquisitions before the end of 2012.
- **BIOCON's IN-105 – Bristol-Myers Squibb** has an option to obtain a global license to market this oral insulin drug if it pans out in Phase II, but Biocon retains the rights in India.
- **CELGENE's Abraxane (albumin-bound paclitaxel for injectable suspension, or nab-paclitaxel)** met the primary endpoint in an 861-patient Phase III trial in pancreatic cancer, improving overall survival when given in combination with **Lilly's Gemzar** (gemcitabine). Details will be presented at the ASCO Gastrointestinal Cancers Symposium in January 2013.
- **DYNAVAX TECHNOLOGIES' Heplisav –** The FDA's Vaccines and Related Biological Products Advisory Committee voted 13-1 that this hepatitis B vaccine is effective but 8-5 (with one abstention) that there are not sufficient safety data. The PDUFA date is February 24, 2013.
- **GLAXOSMITHKLINE's Q-Pan H5N1 vaccine –** The FDA's Vaccines and Related Biological Products Advisory Committee voted unanimously (14-0) to recommend approval of this flu vaccine.
- **GLENVEIGH MEDICAL's Digoxin Immune Fab**, an investigational treatment for severe pre-eclampsia, received fast track designation from the FDA. It already has orphan drug status.
- **IRONWOOD PHARMACEUTICALS' IW-2143 –** The company filed an Investigational New Drug (IND) application for this anti-anxiety drug with the FDA seeking to start a Phase I study in healthy volunteers.

- **KIPS BAY MEDICAL's eSVS** – The FDA said the company can add U.S. sites to an ongoing international study of this surgical mesh for patients undergoing coronary artery bypass graft (CABG) surgery.

- **LILLY, JOHNSON & JOHNSON, and MERCK** are collaborating on a database of worldwide clinical trial sites that will be launched soon. The goal is to help drug developers minimize paperwork and accelerate the new-drug testing processes. The plan is for the database project to eventually include additional major pharmas.

- **MEDTRONIC's CoreValve** – The U.S. Court of Appeals for the Federal Circuit ruled that CoreValve does infringe on **Edwards Lifesciences' Andersen** transcatheter heart valve patent and told the lower court to reconsider Edwards' request for a permanent injunction prohibiting the manufacture and sale of CoreValve in the U.S. However, it is expected that Medtronic will be able to cut a deal with Edwards so CoreValve can be sold in the U.S.

- **MERCK's MK-3475** – The results of a 132-patient Phase Ib trial presented at the Society for Melanoma Research meeting indicated that this investigational PD-1 inhibitor may be effective in advanced melanoma. Within 12 weeks, 51% of the patients in the MK-3475 treatment arm had an objective response, with 9% having a complete response (undetectable). Merck plans to start a Phase II trial of two doses vs. standard chemotherapy.

- **NOVARTIS** – The company's generic manufacturing facility in Colorado, which had gotten an FDA warning letter in December 2011 for violations of cGMP, passed a re-inspection by the FDA. Plants in North Carolina and Quebec, which had the same problem, still need to pass an audit.

- **PFIZER's Mylotarg (gemtuzumab ozogamicin)** – Pfizer voluntarily removed this drug from the market in 2010 after a postmarketing study found a lack of efficacy and increased toxicity, but two recent trials suggest it is beneficial for older patients with acute myeloid leukemia (AML). The new data indicate that one dose of Mylotarg added to chemotherapy significantly improves survival without increased toxicity. The latest trial was published in the ***Journal of Clinical Oncology***.

- **SANOFI's Arava (leflunomide)** – A 105-patient study published in ***Arthritis Research & Therapy*** found that a cumulative dose >19,170 mg of this rheumatoid arthritis drug is associated with a 12-fold increase in liver stiffness vs. methotrexate or other disease-modifying anti-rheumatic drugs taken for at least 24 weeks.

- **SANOFI PASTEUR's Menactra, MenACWY-D** – A pooled analysis of three trials, published in the ***Pediatric Infectious Disease Journal***, found this quadrivalent meningococcal conjugate vaccine was safe and immunogenic for infants given a 2-dose series at age 9 months and 1 year.

- **SAVARA PHARMACEUTICALS' AeroVanc** (dry-powder formulation of vancomycin), an inhaled antibiotic for pulmonary methicillin-resistant *Staphylococcus aureus* (MRSA) infections in cystic fibrosis patients, was granted orphan drug status.

- **SOLIGENIX's SGX-203**, an investigational drug for Crohn's disease in children, received fast track status from the FDA. It already has orphan drug status.

- **TEVA/CEPHALON's Nuvigil (armodafinil)** – An 8-week, 201-patient Phase III study presented at Psych Congress 2012: U.S. Psychiatric and Mental Health Congress found that Nuvigil (which is approved to treat narcolepsy) was also effective as adjunctive treatment for breakthrough depressive symptoms associated with bipolar I disorder, with few adverse events.

- **TRANZYME PHARMA's TZP-102** – The company said a preliminary analysis of the first of two Phase IIb trials found that this once-daily investigational gastroparesis treatment (10 mg and 20 mg), an oral ghrelin agonist, missed the primary efficacy endpoint, failing to reduce four symptoms – nausea, early satiety, bloating, and upper abdominal pain – in diabetics. The second Phase IIb trial of the 10 mg dose TID is still ongoing.

NEWS IN BRIEF

ACELRX PHARMACEUTICALS' Sufentanil NanoTab PCA System (ARX-01) – positive Phase III data

This investigational sublingual patient-controlled analgesia (PCA) drug-device system for post-operative pain met the primary endpoint in a 359-patient Phase III trial, showing superior efficacy in pain control vs. intravenous PCA with morphine at both 24 hours and 72 hours.

In addition, the majority of patients rated the NanoTab System as better than the IV PCA morphine in terms of ease of use and overall satisfaction. The company plans to submit an application to the FDA in 3Q13 (yes, 2013).

Brachytherapy alternative? – radioactive seed implants

A mouse study published in ***Cancer Research***, a journal of the American Association for Cancer Research, suggested in lieu of brachytherapy an alternative radiation delivery method in which radioactive seeds are surgically implanted inside tumors. The new approach, which uses a polymer that forms itself into a radioactive seed after injection into a tumor, requires no surgery and appears highly efficacious and minimally toxic to healthy tissue.

Concierge medicine – a way to solve the PCP shortage?

A study by Accenture found that:

- ~1 in 3 U.S. primary care physicians (PCPs) is considering switching to subscription-based care, such as concierge medicine.
- Recruiting new physicians to hospitals or health systems has become more difficult because of a growing physician shortage.

One possible answer, suggested by Concierge Choice Physicians, is "hybrid concierge medicine," a model where the PCP makes it an option for his or her patients to participate in subscription-based care. The patients can choose to (a) pay a fee for one-on-one, concierge service or (b) continue receiving traditional care from the same physician.

CSL BEHRING's C1-INH – some HAE patients can safely use at home

A study presented in a poster at the American College of Allergy, Asthma, and Immunology annual meeting found that some (not all) patients with hereditary angioedema (HAE) can feasibly and safely self-administer this intravenous drug. Thirteen HAE patients were trained to infuse themselves, and most were able to do that without major problems. In the study:

- Seven patients were trained to use the C1 inhibitor for acute attacks. Three of these never used the product at home after training: one due to cost, one because insurance coverage was lost, and one who decided he would rather not attempt it at home.
- Six patients were trained for prophylactic administration. All of these later used the drug at home.

FDA's 510(k) process – companies dissatisfied

A survey of 128 device company executives commissioned by the MedTech Resource Alliance found:

- 64% either "extremely dissatisfied" or "somewhat dissatisfied" with their experience with the FDA's 510(k) pathway.
- Dissatisfaction was highest among ophthalmic, neurological, and ENT (ear, nose, and throat) device companies.
- Satisfaction was highest among companies that make cardiovascular devices, infection-control and dental devices, and devices for anesthesiology and hospitals.
- The major dissatisfaction was a delay in communication, especially if the FDA ultimately ruled that the product could not be cleared because it wasn't substantially equivalent to a product currently available in the market, the basis by which 510(k) clearances are granted. Nearly half said the FDA paused its review after doing a quick evaluation without reviewing performance data and issued (or said it will issue) a "not substantially equivalent" (NSE) decision.
- Device makers also complained about a perceived lack of scientific expertise at the FDA. Only 7% said that in issuing the NSE ruling, the FDA demonstrated sound scientific issues that the device posed. Nearly 30% described the FDA staff as "extremely confused," and another 27% described the staff as "somewhat confused."

Healthcare IT – primary care adoption strong

A survey, published in ***Health Affairs***, of primary care physicians in 10 countries (U.S., Australia, Canada, and in Europe) found that primary care physicians are making progress in the use of healthcare IT, and U.S. doctors are among the top adopters. The survey results showed that compared to 2009:

- There has been a substantial increase in use in the U.S., but the U.S. still lags behind countries with near-universal adoption, such as Australia, New Zealand, and the U.K.
- There was a 50% increase in electronic health record (EHR) use in the U.S.
- In most countries, doctors with EHRs routinely use electronic order entry for lab tests and prescription drugs.
- 27% of U.S. practices have multifunctional EHRs.
- Electronic exchange of patient information is not yet the norm in any country. In the U.S., this is generally limited to larger practices and integrated health systems.

JOHNSON & JOHNSON and PFIZER's bapineuzumab – J&J not giving up

J&J said it is not scrapping this beta-amyloid inhibitor for Alzheimer's disease despite two failed Phase III trials. Husseini Manji, MD, head of neuroscience for J&J, said the company is "still reviewing the disappointing studies, looking to see whether there are signs [that bapineuzumab could] slow the progression of dementia if taken earlier."

Dr. Manji also said J&J is analyzing bapineuzumab's ability to reduce tau. Furthermore, any decision on what to do with its stake in Elan's planned Prothena spinoff (formerly known as Neotope Biosciences) will wait until J&J further analyzes the bapineuzumab data. (Elan was the original developer of bapineuzumab.)

ROCHE

- **Avastin (bevacizumab).** In the Phase III AVAglio trial, Avastin, when added to radiation and chemotherapy in newly diagnosed glioblastoma, met one of two primary endpoints, prolonging progression-free survival (PFS) 4.4 months (10.6 months vs. 6.2 months for radiation/chemotherapy alone, a 56% improvement, $p<0.0001$).

  An interim analysis of the more important primary endpoint, overall survival, did not show a significant benefit ($p=0.2135$), but the final survival data are not expected until 2013.

  The results were presented at the 17th Annual Meeting of the Society for Neuro-Oncology in Washington DC.

- **Herceptin (trastuzumab).** A study published in the ***Journal of the American College of Cardiology*** found that women with a mean age of 76 who got adjuvant Herceptin had a significantly higher rate of heart failure or cardiomyopathy vs. patients getting no adjuvant therapy (26.7 vs. 16 per 100 patients). The researchers said the risk "remained and increased slightly for those taking anthracycline plus trastuzumab" – 28.2 per 100 patients.

- **Tamiflu (oseltamivir phosphate).** The ***British Medical Journal*** asked Roche to release all of its data on this flu treatment, saying there is no evidence it can actually stop the flu. Peter Gotzsche, leader of the Nordic Cochrane Centre in Copenhagen, called for a boycott of Roche products and for European governments, which have spent millions stockpiling the drug, to sue Roche.

Triple-negative breast cancer – combo of PI3K and PARP inhibitors offers new hope

Simultaneously inhibiting two different pathways – PI3-kinase and PARP – may offer new hope for women with triple-negative breast cancer, according to two studies published in ***Cancer Discovery***, a journal of the American Association for Cancer Research.

PARP inhibitors looked promising in early studies, but their effect was short-lived. Adding a PI3K inhibitor (**Novartis' BKM-120**) increases the cancer's sensitivity to a PARP inhibitor (**AstraZeneca's olaparib**). Jose Baselga, MD, PhD, a hematologist from Massachusetts General Hospital, said, "In a way, with PI3-kinase inhibitors, we are converting BRCA-proficient triple-negative breast cancer into BRCA-deficient breast cancer, and, therefore, these cells become sensitive to PARP inhibition."

When mice were treated with a PI3K inhibitor (again, BKM-120), tumor doubling was delayed from 5 days to 26 days, and combining a PI3K inhibitor and a PARP inhibitor delayed the doubling time to >70 days. Gerburg Wulf, MD, PhD, a hematologist from Beth Israel Deaconess Medical Center, said, "We saw *in vivo* synergy that led to dramatic prolongation of progression-free survival in these mice of more than 2-3 months, which in the life of a mouse is very long. This is an unusual observation that makes us hopeful that it is worthwhile to explore in an early-phase clinical trial."

That trial means a study of two unapproved drugs, which is unusual but not unheard of (it is done rather commonly in HIV and HCV, for example). But the companies are collaborating in a Phase I trial that has already started enrolling patients.

WELLSTAR HEALTH SYSTEM – big focus on healthcare collaborations

WellStar bought the Center for Health Transformation, a healthcare think tank founded in 2003 by former House Speaker Newt Gingrich that went bankrupt. WellStar is keeping the name and plans to reorganize it as a Southeast regional group and invite 20 non-competing, not-for-profit health systems to be charter members and collaborate on ideas to improve healthcare quality, increase access, and lower costs.

WellStar also announced it was forming a non-ownership agreement with **Piedmont Healthcare**, forming the Georgia Health Collaborative, which also will focus on sharing innovative ideas for healthcare delivery and controlling costs.

REGULATORY NEWS

Compounding pharmacy oversight to change

FDA Commissioner Margaret Hamburg, MD, suggested in testimony before a congressional committee that a two-tier approach to regulating compounding pharmacies may be needed. She said traditional compounding of ingredients for specific patients on an as-needed basis needs less oversight than non-traditional compounding that is closer to manufacturing and poses a greater risk.

Senators indicated they would be open to changes in the oversight of compounding pharmacies. Sen. Lamar Alexander (R-TN) said the FDA could be given the power to certify states to regulate large-scale compounders, with the authority to decertify states that don't meet the standards. *Expect new legislation.*

The New England Compounding Center (NECC) and Ameridose are at the heart of the current contamination disaster, but these are not the only compounding pharmacies that have had problems. Last year, a Florida compounding pharmacy was blamed for 12 cases of endophthalmitis from contaminated injections of Roche/Genentech's Avastin, and 11 of those 12 patients permanently lost vision in the affected eye.

FDA's CDRH reorganization

The Center for Devices and Radiological Health (CDRH) reorganized the Office of Device Evaluation (ODE), adding new review divisions – the Division of Surgical Devices and the Division of Neurological and Physical Medicine Devices – as well as 12 new branches. Among the changes:

- Radiological and mammography devices and *in vitro* diagnostics are now in the new Office of In Vitro Diagnostics and Radiological Health. Formerly, *in vitro* diagnostics were regulated by the Office of In Vitro Diagnostics.
- The responsibility for reviewing 30-day notices regarding changes to cardiac devices will shift from the Office of Compliance to ODE's Division of Cardiovascular Devices on January 1, 2013.

Bill could bring some asthma inhalers back

Asthma inhalers using chlorofluorocarbons (CFC) – including **Amphastar Pharmaceuticals/Armstrong Pharmaceuticals' Primatene Mist** (epinephrine metered-dose inhaler) – were banned as of December 31, 2011, to comply with an international air quality treaty, but the House is considering legislation (HR 6190, the Asthma Inhalers Relief Act) that would legalize just Primatene Mist inhalers once again. The bill was approved by the House Energy and Commerce Committee in August 2012.

The bill would allow the remaining Primatene Mist inventories to continue to be sold until the new non-CFC product is approved.

FDA approvals/clearances

- **CERNER's FetaLink+**, which allows clinicians to use iPads or iPhones to access fetal and maternal data in near-real time, was cleared for use.
- **COOK MEDICAL's Zilver PTX**, a paclitaxel-eluting, self-expanding, metal stent, was cleared for use to reopen blocked or narrowed femoropopliteal arteries in patients with peripheral artery disease.
- **CYTOMEDIX's Angel** platelet-rich plasma technology, which allows quick and safe preparation of concentrated plasma in clinical and point-of-care intraoperative environments, received 510(k) clearance.
- **IKARIA's Inomax DSIR device** – New software for this infant drug delivery device received 510(k) clearance.
- **MEDTRONIC's Valiant Captivia stent graft system** received expanded pre-market approval to treat all descending thoracic aorta lesions, except dissections.
- **TELEFLEX's Nylus catheter**, which is delivered peripherally to the central venous system, received 510(k) clearance.
- **TRIVASCULAR's Ovation abdominal stent graft** received premarket approval.
- **VITAL IMAGES' VitreaView** – 3D functionality for this interface between DICOM and non-DICOM images was cleared for use.

FDA recalls/warnings

- **HOSPIRA's Symbiq** – The FDA restricted importation of this drug infusion system, which is produced in Costa Rica.
- **KAISER PERMANENTE** received a warning letter from the FDA, citing a "serious problem involving the conduct of mammography" at its Denver facility. Kaiser did respond, but the FDA said the violations "may be indicative of serious underlying problems" at the facility, and the Agency ***may*** take additional actions, including putting the site under a Directed Plan of Correction, patient notifications, civil money penalties, and even suspension or revocation of its FDA certificate or a court injunction.

- **MINDRAY MEDICAL INTERNATIONAL's A3/A5 Anesthesia Delivery System –** The company initiated a voluntary recall due to the possibility of a system leak resulting from improper seating of the CO_2 absorbent canister gasket.

European regulatory news

- **BRISTOL-MYERS SQUIBB and ASTRAZENECA's Forxiga (dapagliflozin)**, an SGLT2 inhibitor, was approved by the European Commission to treat Type 2 diabetes.
- **NEWLINK GENETICS' HyperAcute-Pancreas Immunotherapy (algenpantucel-L)**, an investigational drug for pancreatic cancer, was granted orphan drug status by the European Commission.
- **NOVARTIS' Agrippal and Fluad –** The Italian Medicines Agency (AIFA) removed its temporary hold on sales of these two seasonal flu vaccines, saying particles found in some of the vials turned out to be due to protein components in the vaccines, which dissolve when shaken and pose no safety risk.
- **ROCHE's Avastin (bevacizumab) –** The Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the use of Avastin-based treatment beyond first progression in metastatic colorectal cancer, recommending that additional data from the ML-18147 study be added to the label.

Regulatory news from other countries

- ***Canada:*** The government has been asked by some provincial health ministers to block generic versions of **Purdue Pharma's OxyContin** (oxycodone) when its patent expires.
- ***India:*** The Central Drugs Standard Control Organization is asking drug companies to recall defective treatments faster.
- ***Japan:*** **Kyowa Hakko Kirin's KW-2246** was submitted to Japanese regulators for approval to treat cancer pain. It is already approved in Canada, the European Union, and the U.S.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
2012		
November 28	**Johnson & Johnson's bedaquiline** to treat patients with multi-drug resistant pulmonary tuberculosis	FDA's Anti-infective Drugs Advisory Committee
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 4	Discussion (no votes) of pediatric development plans for **GlaxoSmithKline's trametinib, Threshold Pharmaceuticals' TH-302, Boehringer Ingelheim's volasertib** (BI-6727), and **Amgen's blinatumomab** (MT-103)	FDA's Pediatric Oncology subcommittee of the Oncologic Drugs Advisory Committee (ODAC)
December 5	Consideration of whether **external counter-pulsating** (ECP) **devices** and **intra-aortic balloon pumps** (IABPs) should remain Class III devices	FDA's Circulatory System Devices Advisory Committee
December 6	Consideration of whether nonroller-type **cardiopulmonary bypass blood pumps** should remain Class III devices	FDA's Circulatory System Devices Advisory Committee
December 7	**Zogenix's Zohydro ER** (hydrocodone bitartrate extended-release) for moderate-to-severe chronic pain	FDA's Anesthetic and Analgesic Drug Products Advisory Committee
December 10	**CoAxia's NeuroFlo** catheter for treating cerebral ischemia	FDA's Neurological Devices Advisory Committee ***Rescheduled from November 1 due to weather***
December 15	**Human Genome Sciences' raxibacumab** to treat inhalation anthrax	PDUFA date
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 bedaquiline** to treat multi-drug resistant tuberculosis	PDUFA date
December 30	**NPS Pharmaceuticals' Gattex** (teduglutide) for short bowel syndrome	PDUFA date
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 21	**Impax Laboratories' Rytary** (IPX-066) for Parkinson's disease	PDUFA date (extended from October 21, 2012)
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 2	**Hemispherx Biopharma's Ampligen** (poly I: poly C12U) to treat chronic fatigue syndrome	PDUFA date
February 10	**Celgene's pomalidomide** for relapsed/refractory multiple myeloma	PDUFA date
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 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 27	**Ariad Pharmaceuticals' ponatinib** for treatment-resistant leukemia	PDUFA date
March 28	**Biogen Idec's BG-12** (dimethyl fumarate) for multiple sclerosis	PDUFA date (extended from December 28, 2012)

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	more 2013	
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 tivozanib** to treat advanced renal cell carcinoma	PDUFA date