TRENDS-in-MEDICINE

November 6, 2011

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…

SHORT TAKES

- **ADHD drugs –** The FDA said a large, recently completed study in children and young adults treated with medication for attention-deficit/hyperactivity disorder (ADHD) did ***not*** show an association between the numerous ADHD medications studied and adverse cardiovascular events such as stroke, MI, or sudden cardiac death.
- **AMGEN's Epogen (epoetin alfa) –** The Centers for Medicare and Medicaid Services (CMS) issued a final rule eliminating (as of payment year 2013) the requirement that kidney dialysis providers maintain hemoglobin >10 g/dL. *This is likely to further reduce use of Epogen in ESRD patients.* *(See CMS/ESRD on page 4 for more details.)*
- **AVANIR PHARMACEUTICALS' Nuedexta (dextromethorphan + quinidine)**, a treatment for pseudobulbar affect, was submitted to European regulators.
- **BAXTER HEALTHCARE's Feiba (Factor VIII inhibitor bypass activity) –** A study published in the ***New England Journal of Medicine*** found that this anti-inhibitor coagulant complex (AICC) reduced joint and other bleeding by 62% in patients with severe hemophilia.
- **BAYER** reportedly wants to in-license drugs in early development to treat chronic kidney disease, eye conditions, and cancer.
- **BIOVEST INTERNATIONAL's BiovaxID**, a personalized cancer vaccine for a rare type of non-Hodgkin's lymphoma, was granted orphan drug status by the FDA.
- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran) –** An article in the German weekly newspaper ***Die Zeit*** said this anticoagulant has been linked to ~50 deaths from bleeding in atrial fibrillation (AFib) patients, though the company maintains the risk:benefit is still in the expected range.
- **CEPHALON's Provigil (modafinil) –** A study, funded by Imperial College London and published in the ***Annals of Surgery***, found that sleep-deprived surgeons who took this narcolepsy drug stayed awake, but they didn't have improved performance on a surgery simulator test.
- **CIRCADIAN TECHNOLOGIES/VEGENICS' VGX-100 –** The FDA gave the company permission to start a Phase I trial of this anti-VEGF-C in patients with late-stage solid tumors, and the company plans to start the trial this year, with results expected in 2H12.
- **DELCATH SYSTEMS' ChemoSat –** The company plans to meet with the FDA about this system that delivers targeted chemotherapy to the liver with the goal of refiling the device by the end of this year.

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- **DFINE** agreed to pay $2.39 million to settle Department of Justice charges that it offered kickbacks to doctors to use its vertebral fracture augmentation devices, though the company continues to claim the allegations were unproven.
- **GLAXOSMITHKLINE's Avandia (rosiglitazone)** – The FDA reminded doctors and patients that anyone taking this Type 2 diabetes drug should be enrolled in the Avandia-Rosiglitazone Medicines Access Program if they want to continue receiving the drug. After November 18, 2011, Avandia will no longer be available through retail pharmacies and will only be available by mail order through specially certified pharmacies participating in the program.
- **Idiopathic pulmonary fibrosis (IPF)** – The National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health (NIH), stopped one arm of the three-arm, multicenter PANTHER-IPF trial after the interim results showed that participants with IPF on a commonly used triple-drug therapy – prednisone, azathioprine, and N-acetylcysteine (NAC) – had worse outcomes than those who received placebo.
- **IMMUPHARMA's Lupuzor (rigerimod)** – The FDA gave the company the green light to begin a Phase III trial of this investigational lupus drug and gave it fast track status. However, the company still needs a partner since **Cephalon** gave up on Lupuzor.
- **MEDIVATION and ASTELLAS' MDV-3100** – Medivation reported that this androgen receptor signaling inhibitor extended median survival by 4.8 months in the Phase III AFFIRM trial in advanced prostate cancer patients who had received prior chemotherapy. The increased survival was so good that the trial was halted early, and all patients were offered the drug. The companies plan to submit the drug to the FDA in 2012.
- **MEDTRONIC's MiniMed Paradigm** – The FDA gave Medtronic an investigational device exemption (IDE) to conduct an in-home trial of this insulin pump in Type 1 diabetics. The trial is the second stage of Medtronic's ASPIRE trial and will also test the company's **Enlite** glucose sensor as part of the system.
- **MERCK's Vytorin (ezetimibe + simvastatin)** – The FDA's Endocrinologic and Metabolic Drugs Advisory Committee reviewed the findings of the SHARP trial and voted unanimously that this cholesterol-lowering medication should be approved to prevent heart disease in chronic kidney disease patients not yet on dialysis, but they rejected (by a vote of 10-6) use in dialysis patients.
- **PFIZER's Lipitor (atorvastatin)** – The company said it will seek approval of a non-prescription (over-the-counter) form of this cholesterol-lowering medication.
- **PLURISTEM THERAPEUTICS' PLX stem cells** – The company said a Phase I trial in critical limb ischemia showed positive results, improving amputation-free survival at 12 months.
- **VIVUS' Qnexa (phentermine + topiramate)** – The FDA accepted the company's resubmission of this diet drug. The new PDUFA date is April 17, 2012.

NEWS IN BRIEF

Cancer metastases – new clue to formation

Canadian researchers identified a mechanism of metastasis that they said could lead to a way to block tumor growth. The findings, which were published in the journal ***Cancer Research***, suggested that the macrophage cell surface protein S100A10 may be essential to metastatic tumor development. The researchers found that tumors will not grow without the help of macrophages; and, at least theoretically, blocking either the macrophages or S100A10 could slow or halt tumor growth.

EXELIXIS' cabozantinib – no SPA for Phase III trials

The company plans to start two Phase III trials of this drug for metastatic castration-resistant prostate cancer (CRPC) but ***not*** under an FDA Special Protocol Assessment (SPA).

- The double-blind **'306 trial** will enroll 246 patients with moderate-to-severe bone pain despite optimized opioids who have failed both docetaxel and **Johnson & Johnson's Zytiga** (abiraterone), and the primary endpoint will be pain relief at Week 9 that is confirmed at Week 15, with overall survival a secondary endpoint. Bone scans will also be a secondary endpoint. The trial will compare cabozantinib to mitoxantrone/prednisone and will be conducted in the U.S., Canada, and the U.K.
- The global **'307 trial**, which is expected to start in 1H12, will have overall survival as its primary endpoint. It will compare cabozantinib to prednisone in patients who failed docetaxel and Zytiga.

IGF-1R monoclonal antibodies – an uncertain future

Two studies of insulin-like growth factor type 1 receptor agents were published in the ***Journal of Clinical Oncology***, and the results showed modest activity, but researchers said pharma interest has evaporated.

1. **Roche's R-1507.** A study in 115 patients with recurrent/refractory Ewing sarcoma showed only modest activity with

R-1507, with a response rate of 10%, a 29-week median duration of response, overall survival of 7.6 months, and low toxicity. Roche/Genentech apparently lost interest in this.

2. **Pfizer's figitumumab (CP-751,871).** A Phase I/II study in 107 patients given 30 mg/kg monthly, which showed partial responses in 15 patients, stable disease in 25, a median duration of response of 4.7 months, median PFS of 1.9 months, and median overall survival of 8.9 months. Pfizer no longer has this on its pipeline list.

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- **Nucynta (tapentadol extended-release)** was submitted to the FDA for treatment of adults with diabetic peripheral neuropathy.
- **Xarelto (rivaroxaban)** was approved right on schedule by the FDA to prevent strokes in patients with AFib. The FDA did not require a postmarketing study of switching patients to/from warfarin. However, there is a boxed warning (as with other anticoagulants) that patients should not discontinue use without a discussion with their doctor.

NPS PHARMACEUTICALS' Gattex (teduglutide) – positive results but two deaths

Data from the long-term, open-label STEPS-2 trial were presented at the American College of Gastroenterology (ACG) meeting, and this GLP-2 (*yes, GLP-2, not GLP-1*) demonstrated clinically meaningful reductions in parenteral nutrition (PN) and IV fluid volume in adults with short bowel syndrome. NPS plans to submit Gattex to the FDA by the end of 2011. Three patients in the trial (all in Poland) developed cancer, and two of them died, but the data safety monitoring board reviewed them and did not make any changes to the ongoing trial. The cases included:

- A metastatic adenocarcinoma of probable gastrointestinal origin that resulted in death. This patient had a prior history of Hodgkin's disease treated with chemotherapy and radiotherapy. A neoplasm was discovered after 313 days of therapy. At six months before starting Gattex, a CT showed a markedly enlarged liver with a focal lesion of unclear origin.
- A non-small cell lung cancer carcinoma that resulted in death. This 64-year-old patient was a long-term heavy smoker.
- A squamous cell carcinoma of the lung. This patient, who did not die, was 74 years old and had a history of smoking.

Osteoarthritis – long-term therapy being investigated

University of Florida researchers, under a grant from NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases, is conducting preclinical studies of gene therapy using adeno-associated viruses (AAVs) to create a joint-targeted, one-time, long-term treatment for osteoarthritis. The idea is that the gene therapy approach would allow continued production of therapeutic protein within the joints, actually changing the course of the disease.

Pacemakers – may be okay in metal detectors

German researchers reported that it is safe for newer-model pacemakers and implantable cardioverter-defibrillators (ICDs) to go through metal detector security screening. In the study, published in the ***Annals of Internal Medicine***, the researchers simulated screening of 388 patients with ICDs, even doing prolonged swipes with hand-held metal detectors, and found no abnormalities in device function. However, they cautioned that the study needs to be confirmed in real-world settings.

PFIZER's Chantix (varenicline) – new suicidality questions raised

Researchers who analyzed data from the FDA's Adverse Event Reporting System (AERS) came to a different conclusion on the psychiatric side effects of this smoking-cessation drug. Two FDA studies found that Chantix did not increase the risk of psychiatric hospitalization, but the new outside research, which was published in the Public Library of Science journal ***PLoS ONE***, found Chantix increased the risk of suicide 8-fold.

The researchers reviewed 3,249 reports of serious self-injury or depression linked to Chantix, **GlaxoSmithKline's Zyban** (bupropion), and nicotine replacement products. They found that 2,925 cases (90%) of suicidal behavior or depression reported to the FDA were related to Chantix, even though the drug was on the market for only 4 of the 13 years studied. There were 299 cases related to Zyban and 95 cases to nicotine replacement products. Study co-author Curt Furberg, MD, PhD, from Wake Forest Baptist Medical Center said, "Chantix is associated with more suicidal behavior reports than any other smoking-cessation drug on the U.S. market. The risks simply outweigh the benefits."

SHIRE's Replagal (agalsidase) – resubmitted to FDA

This drug to treat Fabry disease is being resubmitted to the FDA along with some new data. Shire withdrew the application last year before the FDA acted on it, but the FDA has allowed Shire to provide patients with the drug for free during

the shortage of **Genzyme's Fabrazyme**. Shire officials said 2,800 patients worldwide are taking Replagal now, and the company will be able to accommodate "a modest number" of new patients when and if a new plant is approved by the FDA.

TNF inhibitors – FDA ups surveillance of cancer

The FDA ordered drugmakers to report malignancy cases among patients age ≤30 on a TNF inhibitor for rheumatoid arthritis (or anything else). The Agency reminded the companies that they must submit these adverse events within 15 days of learning of them. The FDA also urged doctors to be "vigilant" in monitoring for malignancies in these patients.

REGULATORY NEWS

CMS issues final rule on HOPD and ASC payment policies and rates

CMS issues a final rule – but there is still a comment period until January 3, 2012 – that will update payment policies and payment rates for services furnished to Medicare beneficiaries in hospital outpatient departments (HOPDs) and ambulatory surgical centers (ASCs) beginning January 1, 2012.

CMS projects that total payments to more than 4,000 hospitals will be ~$41.1 billion in calendar year 2012 (CY2012) under the Outpatient Prospective Payment System (OPPS), and that the ~5,000 Medicare-participating ASCs will be paid ~$3.5 billion in the same period.

The final rule also establishes an electronic reporting pilot program to allow additional hospitals to report clinical quality measures in 2012 for purposes of participating in the Medicare Electronic Health Record Incentive Program.

Among the provisions in the final rule:

- OPPS payments will increase 1.9%.
- Designated cancer hospitals will get an 11.3% increase.
- More attention to the issues affecting rural hospitals.
- Pay for the acquisition and pharmacy overhead costs of separately payable drugs and biologicals, other than new drugs and biologicals that have pass-through status, at an average sales price (ASP) + 4%.
- Increase payments to ASCs by 1.6%.

CMS issues new ESRD policies and payment rates

CMS issued a final rule updating Medicare policies and payment rates for 5,503 dialysis facilities paid under the End Stage Renal Disease (ESRD) Prospective Payment System (PPS) that was first implemented in CY2011. The rules go into effect January 1, 2012, and will affect payment rates in payment years (PYs) 2013 and 2014. Key points include:

- **Payment rates for dialysis treatments** will increase 2.1% in CY2012, the second year of a 4-year transition to a fully bundled payment system. However, 90% of facilities chose to skip the transition and be paid entirely under the new system.
- The **quality incentive program** (QIP) is strengthened, with payments to individual facilities reduced if the facility does not achieve a certain total performance score on two anemia management measures and one measure of dialysis adequacy.
- **Anemia management:**
  - **For PY2013**, the requirement that dialysis patients have a hemoglobin >10 g/dL is eliminated. CMS said this change is "consistent with the recent labeling for ESAs" approved by the FDA. CMS will give equal weight to the two finalized measures: (1) hemoglobin >12 g/dL and (2) Urea Reduction Ratio (URR) of ≥65%. Patrick Conway, MD, CMS chief medical officer and director of CMS's Office of Clinical Standards & Quality, said, "This patient-centered approach should result in better treatment outcomes. We plan to monitor hemoglobin levels by facility and to transparently share this information with consumers."
  - **For PY2014**, CMS is retaining one anemia management measure (hemoglobin >12 g/dL) and the URR of ≥65% but is also adopting four new measures:
    1. Percent of patients receiving treatment through an arteriovenous fistula or catheter.
    2. Whether the facility reports certain dialysis-related infections to the Centers for Disease Control & Prevention's National Healthcare Safety Network.
    3. Whether the facility administers a patient experience of care survey.
    4. Whether the facility monitors phosphorus and calcium levels on a monthly basis.

Medicare doctor pay saga continues

CMS issued its final physician payment rule for 2012, and doctors will receive 27.4% less next year unless Congress intervenes once again (as it has 10 times before). Health and Human Services Secretary Kathleen Sebelius said the Obama administration will not allow such deep cuts to actually go into effect, and she urged Congress to pass another "doc fix" bill to avert the cuts.

Until the sustainable growth rate (SGR) – which CMS is mandated to use to figure doctor pay under Medicare – is revised, this situation will continue to occur.

FDA asks for medical device labeling feedback

The FDA is asking for public comments, particularly from healthcare providers, on its system for medical device labels to help identify the most effective labeling format. The deadline for comments is January 3, 2012.

FDA says it *is* innovative

In an internal memo to staff within the FDA's Center for Drug Evaluation and Research (CDER), senior FDA officials defended the Agency's record on innovation, writing, "You may have seen news reports or statements by industry that we are not 'innovative' or that we make it too hard for companies to get a new product on the market. But these broad-brush statements are, in most cases, inaccurate and unfair. They often lack important context that would explain our intentions and the work we do."

The memo accompanied the release of an FDA report that showed that CDER and the Center for Biologic Evaluation and Research (CBER) together approved 35 new molecular entities (NMEs) in FY2011, including **Vertex's Incivek** (telaprevir) and **Merck's Victrelis** (boceprevir) for HCV, **Human Genome Sciences' Benlysta** (belimumab) for lupus, **Bristol-Myers Squibb's Yervoy** (ipilimumab) for melanoma, and **Pfizer's Xalkori** (crizotinib) for lung cancer. The Agency said, "The speed and efficiency with which these products were approved speaks directly to our staff and our high-quality reviews. It also demonstrates our willingness to exercise regulatory flexibility and creative approaches to help industry meet our standards – without lowering them."

The FDA also pointed out that it expedited the approval of many products by streamlining clinical trial requirements to permit smaller, shorter, or fewer studies. Highlights in the report included:

- Sixteen of the 35 NMEs were approved under the priority review program.
- Thirty-four of the 35 NMEs were approved on or before the PDUFA date.
- Three received accelerated approval.
- The majority were approved in the first cycle and did not involve additional FDA requests for information and a second cycle of review.

Supreme Court lets medical device judgment stand

The U.S. Supreme Court left intact a ruling in *Stryker vs. Bausch* that let a woman sue **Stryker** over a recalled artificial hip, rejecting Stryker's appeal and refusing to strengthen the limits on patient lawsuits against medical device manufacturers that resulted from a 2008 ruling that said patients generally can't sue over product liability for products that were approved by the FDA under a premarket approval (PMA).

FDA approvals/clearances

- **ABBOTT LABORATORIES' Xience Prime** drug-eluting stent.
- **DELTEX MEDICAL's CardioQ-EDM**, an updated patient monitor.
- **EDWARDS LIFESCIENCES' Sapien** percutaneous aortic valve was approved for use in inoperable patients with a calcified aortic annulus, but the label says a surgeon should be involved in determining whether the patient meets the criteria. Patients will be entered into a new national registry.
- **MEDTRONIC's Assurant** balloon-expandable iliac artery stent.
- **MELA SCIENCES' MelaFind** – The PMA for this device for detecting skin cancer was approved.
- **PACIRA PHARMACEUTICALS' Exparel (bupivacaine liposome injectable suspension)**, a non-opioid analgesic, was approved for postsurgical pain relief.
- **ROCHE's hepatitis B blood test** to determine if a hepatitis B infection is acute or recent.
- **TRIVASCULAR's Ovation**, a 20 mm abdominal aortic aneurysm stent graft system, was approved for use in iliac or femoral arteries as a Humanitarian Use Device (HUD), which limits use to <4,000 Americans each year. What makes it unique is the small diameter of the stent and the narrow delivery catheter (4.7 mm). A portion of Ovation's metal stent has ring-shaped channels that, after the device is in place in the aorta, are injected with a polymer, expanding the endograft against the aorta to create a seal.

FDA recalls

CAREFUSION's EnVe Ventilators – A Class I recall was initiated because of the potential for defects that could interrupt patient ventilation, potentially leading to hypoxia, serious neurological injury, or death. The company is coordinating hardware and software updates for the affected ventilators.

European regulatory actions

- **CELLDEX THERAPEUTICS' rindopepimut**, an experimental immunotherapy for glioblastoma, was granted orphan drug status. The company plans to start a Phase III trial later this year. Rindopepimut already has both orphan drug and fast track status with the FDA.
- **DISCOVERY LABORATORIES' KL4 surfactant**, an experimental cystic fibrosis drug, received orphan drug status from the European Medicines Agency (EMA).

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

BOEHRINGER INGELHEIM's Pradaxa (dabigatran), a blood thinner to prevent strokes in AFib, was recommended for use by the National Health Service, but NICE said a decision to use it should be made after an "informed discussion about the risks and benefits" vs. warfarin.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	November 2011	
November 12	**Alimera Sciences' Iluvien** (SR fluocinolone acetonide implant) for DME	PDUFA date
November 16	**Pneumococcal 13v vaccine** safety and immunogenicity in adults >age 50	FDA's Vaccines and Related Biological Products Advisory Cmte
November 16	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for IBS-D	FDA's Gastrointestinal Drugs Advisory Committee
November 17	**5-HT4 agonists** for IBS-C	FDA's Gastrointestinal Drugs Advisory Committee
November 17	**Organogenesis' Apligraf**, an oral therapy for treating surgically created gingival and alveolar mucosal surface defects in adults	FDA's Cellular, Tissue, and Gene Therapies Advisory Committee
November 18	**Regeneron's Eylea** (aflibercept, VEGF Trap-Eye) for wet AMD	PDUFA date
November 27	**Transcept Pharmaceuticals' Intermezzo** (zolpidem tartrate) for insomnia	PDUFA date
	December 2011	
December tba	**Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to be completed	Company announcement or medical conference presentation
December 1	Review of **risk evaluation and mitigation strategies (REMS), including iPLEDGE for isotretinoin**	FDA's Drug Safety and Risk Management Dermatologic and Ophthalmic Drugs Advisory Committees meeting jointly
December 5	Using scientific research data to support a **pediatric medical device claim**	FDA public workshop
December 7	**Pfizer's Inlyta** (axitinib) for advanced renal cell carcinoma and **Affymax's peginesatide injection** for anemia in chroic renal failure dialysis patients	FDA's Oncologic Drugs Advisory Committee (ODAC)
December 7	Expanding the indication for **Medtronic's CRT-D devices** to symptomatic NYHA Class II patients with LBBB, QRS ≥120 ms, and LVEF ≤30%	FDA's Circulatory System Devices Advisory Committee
December 8	**CardioMEMS' CardioMEMS HF Pressure Measurement System**, a permanently implantable pulmonary arterial pressure measurement system	FDA's Circulatory System Devices Advisory Committee
December 8	**Antares Pharma's Anturol** (transdermal oxybutynin ATD gel), for OAB	PDUFA date
December 8	**Bayer's Yaz, Yasmin, and Beyaz** (drospirenone) blood clot safety review	FDA's Reproductive Health Drugsand Drug Safety and Risk Management Advisory Committees meeting jointly
December 9	**Johnson & Johnson/Janssen's Ortho Evra** (norelgestromin/ethinyl estradiol transdermal system) blood clot safety review	FDA's Reproductive Health Drugs Drug Safety and Risk Management Advisory Committees meeting jointly
December 12	**Alexza Pharmaceuticals' Adasuve** (loxapine inhalation powder), for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. Pulmonary safety is the key concern.	FDA's Psychopharmacologic Drugs Advisory Committee
December 13	**Endo Pharmaceuticals' Opana** (extended-release oxymorphone), a painkiller	PDUFA date
	Other 2011 events of interest	
4Q11	**Ophthotech's ARC-1905** primary endpoint results in Phase I trial in dry AMD	Company announcement or medical conference presentation
	2012	
January	**Pfizer's Prevnar 13** (PCV13), a pneumococcal vaccine for adults	PDUFA date
January 3	**Medical device labeling** feedback is sought	FDA deadline for public comment
January 28	**Bristol-Myers Squibb and AstraZeneca's dapagliflozin**, a first-in-class SGLT2 inhibitor for Type 2 diabetes	PDUFA date
January 28	**Eli Lilly, Amylin Pharmaceuticals and Alkermes' Bydureon** (weekly exenatide XR), an injectable drug for Type 2 diabetes	FDA decision date
February	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation
February 4	**Alexza Pharmaceuticals' Adasuve** (loxapine inhalation powder), for the acute treatment of agitation associated with schizophrenia or bipolar I disorder	PDUFA date
February 17	**Corcept Therapeutics' Corlux** (mifepristone) for Cushing's syndrome	PDUFA date
February 28	**Pfizer's axitinib** for advanced renal cell carcinoma	PDUFA date (*approximate*)
March tba	**Anti-nerve growth factor (NGF)** drug class safety review	FDA's Arthritis Advisory Committee – originally scheduled for September 13, 2011, but postponed indefinitely, now March 2012
March 6	**Discovery Labs' Surfaxin** (lucinactant), a therapy for infant respiratory disease	PDUFA date
March 27	**Affymax and Takeda's peginesatide** for anemia	PDUFA date
March 28	**Edwards Lifesciences' Sapien** transcatheter aortic valve	CMS expected to publish NCD decision memo
April 17	**Vivus' Qnexa** (phentermine + topiramate) for weight loss	PDUFA date for resubmission
April 26	**Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in prostate cancer	PDUFA date
April 27	**Salix Pharmaceuticals and Progenics Pharmaceuticals' Relistor** (methylnaltrexone injection) for opioid-induced constipation	PDUFA date
April 29	**Vivus' avanafil** for erectile dysfunction	PDUFA date
April 30	**Baxter and Halozyme's HyQ** for immunodeficiency	PDUFA date
June	**Forest Laboratories and Ironwood Pharmaceuticals' linaclotide** for IBS-C	PDUFA date
June 26	**Edwards Lifesciences' Sapien** transcatheter aortic valve	CMS final NCD expected