TRENDS-in-MEDICINE

February 24, 2013

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 **Advances in Genome Biology and Technology** (AGBT) meeting in Marco Island FL.

SHORT TAKES

- **ABBOTT LABORATORIES** is collaborating with **Johnson & Johnson/Janssen Biotech** and **Pharmacyclics** to test whether the fluorescence in-situ hybridization (FISH) diagnostic test Abbott is developing will identify patients with a high-risk subtype of chronic lymphocytic leukemia (CLL) – patients with a deletion within a specific chromosome that makes them more likely to respond to J&J's ibrutinib (PCI-32765).

- **AFFYMETRIX's CytoScan** cytogenetics platform was submitted to the FDA.

- **Bariatric surgery –** A study published in ***JAMA Surgery*** found that bariatric surgery patients had the same or slightly higher healthcare costs over six years vs. obese people with health problems who did not undergo the procedure, suggesting that the surgery does not have long-term cost savings.

- **BIOGEN IDEC's Tysabri (natalizumab) –** A 20-patient study published in ***JAMA Neurology*** found that off-label use of Tysabri in children with severe multiple sclerosis reduced relapses and brain lesions seen on MRI scans. The mean annualized relapse rate for Tysabri patients was 0.4 vs. 3.77 before starting Tysabri ($p<0.001$). New T2/fluid attenuated inversion recovery (FLAIR) lesions decreased from a mean of 7.8 before Tysabri to 0.5 on the drug ($p=0.001$).

- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran) –** A study published in the ***New England Journal of Medicine*** found this direct thrombin inhibitor was non-inferior to warfarin for extended secondary prevention of venous thromboembolism (VTE). The recurrent VTE rate was 1.8% vs. 1.3%. Major/clinically relevant bleeding was significantly less with Pradaxa, but there were more cases of acute coronary syndrome (ACS) with Pradaxa (0.9% vs. 0.2%).

- **CHELSEA THERAPEUTICS' Northera (droxidopa) –** The company said the FDA has decided that the company can resubmit the original trial data on this investigational treatment for symptomatic neurogenic orthostatic hypotension and does not need to do another clinical trial. In March 2012 the FDA rejected Northera, requesting another clinical trial prior to approval, but the company appealed to the FDA's Office of New Drugs over the FDA's rejection. Chelsea plans to resubmit the new drug application (NDA) in 2Q13.

- **CHIASMA's Octreolin (octreotide)** – **Roche** is collaborating with Chiasma on this investigational oral drug for acromegaly and neuroendocrine tumors. Chiasma will handle development through the ongoing Phase III acromegaly trial.

- **Electronic health records (EHRs)** – A report issued by ***Black Book Rankings*** found that up to 17% of physician practices using an EHR are planning to switch vendors by the end of 2013. The problem appears to be that the doctors bought systems that were "immature" and don't meet the government's performance standards.

- **EXACT SCIENCES' Cologuard**, a DNA test that uses stool samples to screen for colorectal cancer – The company submitted the second module (of three modules) of its PMA application to the FDA. The third module from the DeeP-C pivotal clinical trial is expected to be available in March 2013.

- **EXELIXIS' Cometriq (cabozantinib)** – Exelixis entered into a three-year agreement under which **Swedish Orphan Biovitrum** will be the exclusive distributor of this drug in the European Union once the European Medicines Agency (EMA) approves it – but just for metastatic medullary thyroid cancer, not for other future indications.

- **FERRING PHARMACEUTICALS' MVI (controlled-release misoprostol vaginal insert)** – A study by University of California, Irvine, researchers, presented at the Society for Maternal-Fetal Medicine, found that this investigational misoprostol suppository, which is used to induce labor, works faster (11 hours faster) than **Forest Laboratories' Cervidil** (dinoprostone).

- **Flu vaccine** – The Centers for Disease Control and Prevention (CDC) said this season's flu shot was only 9% effective in protecting seniors against the flu and only 56% effective for all age groups. *Some protection is better than none was how CDC tried to spin this.*

- **FRESENIUS' HES (hydroxyethyl starch)** – A new, 38-trial meta-analysis of 10,868 patients, published in the ***Journal of the American Medical Association***, found that this blood volumizer used to help resuscitate critically ill patients increases the risk of death and kidney damage. The new analysis was undertaken after scientific misconduct was alleged by a German scientist who had conducted seven HES trials. Without those trials, the researchers concluded that HES is *not* safe.

- **GILEAD SCIENCES' Viread (tenofovir)** – Gilead and **Teva** settled a patent dispute just days before a patent trial was to begin. The settlement will allow Teva to introduce a generic tenofovir on December 15, 2017.

- **Glaucoma** – After reviewing comparative evidence for medical, laser, and surgical treatments, the U.S. Preventive Services Task Force (USPSTF) said, in a draft Recommendation Statement published in the ***Annals of Internal Medicine***, that it is still unclear which approach is better for open-angle glaucoma. USPSTF said there is high-level evidence that all three treatments decrease intraocular pressure (IOP), but the comparative efficacy of the different treatments was unclear, and the direct effect of treatment on visual impairment was uncertain. The draft Recommendation Statement is open for comment until March 18, 2013.

- **GLAXOSMITHKLINE and THERAVANCE's Anoro [umeclidinium bromide (GSK-573719) + vilanterol, UMEC/VI]** – The company said the FDA accepted the NDA for this daily treatment for chronic obstructive pulmonary disease (COPD), a combination of a long-acting muscarinic antagonist and a long-acting beta-2 agonist. The PDUFA date is December 18, 2013.

- **INSIGHTEC's ExAblate Neuro** – The FDA gave its approval for a study of this MR-guided focused ultrasound system to treat essential tremor through the intact skull without incisions or ionizing radiation. The company expects to start enrolling patients by mid-2013.

- **Isotretinoin** – A study of >45,000 women published in ***JAMA Dermatology*** found that this acne drug does ***not*** raise the risk of inflammatory bowel disease (IBD) in women.

- **JOHNSON & JOHNSON's Simponi (golimumab)** – A Phase III trial published in the ***Annals of the Rheumatic Diseases*** found that rheumatoid arthritis patients had a significant and rapid response to this intravenous TNF inhibitor + methotrexate, with 58.5% of patients achieving ACR20 by Week 14 vs. 24.9% of patients on placebo + methotrexate. ACR20 was achieved by Week 2 in 33.2% of Simponi patients vs. 11.7% of placebo patients.

- **Neuroblastoma** – Researchers at Dana-Farber Cancer Institute reported in ***Cancer Discovery*** on their finding that neuroblastomas containing MYCN amplification are associated with a poor prognosis but are sensitive to a new class of drugs, BET bromodomain inhibitors. In preclinical studies, a BET bromodomain inhibitor developed at Dana-Farber prolonged survival.

- **PEREGRINE PHARMACEUTICALS' bavituximab** – The company released revised data from a 121-patient Phase II trial of this investigational lung cancer drug, saying the survival outcome was not as statistically significant as reported in September 2012. The revised survival is 11.7 months for 3 mg/kg bavituximab + chemo (docetaxel) vs. 7.3 months for chemo alone or bavituximab 1 mg/kg + chemo. The company plans to discuss development plans with the FDA.

- **PFIZER's Toviaz (fesoterodine)** – In a study published in the ***Journal of the American Geriatrics Society*** this anti-muscarinic drug was effective and well-tolerated by elderly patients with overactive bladder (OAB). The mean number of urgency episodes per 24 hours decreased by 3.9 at Week 12 with Toviaz vs. a decrease of 2.5 with placebo. In addition, the number of micturitions, nocturnal micturitions, and incontinence pads used over 24 hours decreased significantly with fesoterodine vs. placebo.

- **PHYTOPHARM's Cogane (PYM-50028)** missed the primary and the secondary endpoints in a 400-patient Phase II trial in Parkinson's disease, showing no benefit vs. placebo in reducing symptoms or slowing neurodegenerative progression. The company said all other R&D projects with the drug are on hold until the findings are reviewed.

- **PLURISTEM THERAPEUTICS' PLacental eXpanded cells** – The FDA granted orphan drug status to this investigational aplastic anemia treatment.

- **Prosthetics** – Swiss researchers announced that they have developed a "smart" artificial hand that allows amputees to feel what they are touching or holding. The limb is 1-2 years away from broad testing.

- **QUATRX PHARMACEUTICALS and SHIONOGI's ospemifene** – In a 600-patient study published in the journal ***Menopause***, taking a 60 mg daily dose of this investigational SERM (selective estrogen receptor modulator) for 12 weeks was as effective as low-dose oral estrogen in reducing painful intercourse. The ospemifene women had significantly lower vaginal pH and less vaginal dryness and reported less pain during sex vs. placebo. The drug has already been submitted to the FDA, and the PDUFA date is February 26, 2013.

- **REPROS THERAPEUTICS' Androxal (enclomiphene citrate)** – Before releasing the data from a Phase III trial of this drug for normalizing testosterone and luteinizing hormone levels in men with secondary hypogonadism, the company found that one of the 16 sites had very different baseline characteristics. The company said the FDA has agreed that the company can drop those patients from its analysis and enroll an additional 40 patients. However, the FDA also is requiring the company to conduct a study that will compare the data from the outlier site to the other sites.

- **SANOFI/GENZYME's eliglustat tartrate**, an oral investigational therapy for Gaucher disease, met the primary endpoint in two Phase III trials, one vs. placebo and one vs. Sanofi's Cerezyme (imiglucerase injection). In both studies, spleen volume was significantly decreased with eliglustat vs. control.

- **SANOFI and ZEALAND PHARMA's lixisenatide** – The company said the FDA accepted this once-daily oral GLP-1 agonist for diabetes for review. The brand name for Europe is Lyxumia, but the U.S. brand name has not been announced.

- **VIIV HEALTHCARE's dolutegravir**, an investigational integrase inhibitor for HIV, was granted priority review by the FDA. The PDUFA date is August 17, 2013.

NEWS IN BRIEF

Chemotherapy – off-label drug use common

A study by University of Chicago researchers using a national prescription database from 2010, published in the ***Journal of Clinical Oncology***, found that 30% of all injected or infused chemotherapy treatments include a drug that is not FDA-approved for that indication. However, almost half of these off-label uses were in accordance with National Comprehensive Cancer Network (NCCN) guidelines. The total cost of chemotherapies in 2010 was ~$12 billion – $7.3 billion for on-label uses and $4.5 billion for off-label drugs, with $2.5 billion of the off-label use not in the NCCN guidelines.

Dialysis – treatment improvements

- **Fistulas better than catheters or grafts.** A meta-analysis of 67 studies of ~600,000 dialysis patients, published in the ***Journal of the American Society of Nephrology***, found that fistulas are the safest way to access blood. Dialysis patients using central venous catheters had a 53% higher risk of death, a doubled risk of fatal infection, and a 38% higher risk of cardiovascular problems vs. patients using arteriovenous fistulas for access to blood. And arteriovenous graft patients had an 18% higher risk of death and a 36% higher risk of serious infection vs. fistula patients.

- **On-line hemodiafiltration (OL-HDF).** A 906-patient study published in the ***Journal of the American Society of Nephrology*** found that this new dialysis method – high convective transport – removed more toxins than conventional hemodialysis, reduced all-cause death by 30% (the primary

endpoint), and decreased the risk of fatal stroke and fatal infections. The researchers estimated that switching eight patients to OL-HDF from conventional hemodialysis would prevent one death a year. At three years:

- All-cause mortality was 18.6% with OL-HDF vs. 27.1% for hemodialysis (p=0.01).
- Cardiovascular mortality was 33% less with OL-HDF, but the difference was not statistically significant.
- Fatal strokes were significantly lower with OL-HDF (p=0.03).
- All-cause hospital admissions were significantly lower with OL-HDF (p=0.001).
- Infection-related mortality was 55% lower with OL-HDF (p=0.03).

GILEAD SCIENCES' sofosbuvir (GS-7977) – positive results from fourth Phase III HCV trial

The company reported top-line results from the Phase III FUSION trial in treatment-experienced patients with hepatitis C virus (HCV) genotypes 2 or 3, saying sofosbuvir, a nucleotide inhibitor, demonstrated superiority vs. control. The company plans to submit the drug to the FDA in 2Q13.

FUSION Trial Results		
Measurement	**Sofosbuvir n=201**	**Historical control**
Primary endpoint: SVR12 at 12 weeks	50% (p<0.001)	25%
SVR12 at 16 weeks	73% (p<0.001)	---
Genotype 2 (n=74)		
SVR12 at 12 weeks	86%	---
SVR12 at 16 weeks	94%	---
Genotype 3 (n=127)		
SVR12 at 12 weeks	30%	---
SVR12 at 16 weeks	62%	---
Patients with compensated cirrhosis (n=68)		
SVR12 at 12 weeks	31%	---
SVR12 at 16 weeks	66%	---

Heart failure – positive news for gene therapy

In a 17-patient, open-label, Phase I, first-in-man study published in ***Circulation Research***, a journal of the American Heart Association, injections of stromal cell-derived factor-1 (SDF-1) into the myocardium of patients with ischemic heart disease showed positive results. At four months, all cohorts showed improvements in the six-minute walk test, quality of life, and NYHA Class; and at 12 months the improvements in symptoms were maintained.

This treatment signals stem cells to go to injured tissue and repair it, rather like a homing signal. The findings add to evidence suggesting that SDF-1 can increase blood flow around an area of damaged tissue that has been deemed irreversible by other testing.

In an accompanying editorial, the commentator said the study showed the safety and feasibility of the strategy but noted the small number of patients and added that there were a host of design issues that "tempers enthusiasm," including several parameters trending toward a worsening state at four months.

Hip implants – failure rate higher for women

A large U.S. registry study of 35,140 Kaiser Permanente hip implant patients – conducted by Southern California Permanente Research Group in San Diego, funded by the FDA, and published in ***JAMA Internal Medicine*** – found that the all-cause failure rate was 29% higher for women than men (2.3% vs. 1.9%, HR 1.29).

- The risk of failure was highest for aseptic revisions (HR 1.32) compared with septic failure (HR 1.17).
- Larger femoral head sizes (≥36 mm) appeared especially problematic for women (HR 1.49).
- Metal-on-metal implants were much worse for women vs. men (HR 1.97), but women got metal-on-metal implants much less often than men.

Laser surgery – litigation on the rise

A retrospective study of a large legal database by Harvard Medical School researchers – published in ***JAMA Dermatology*** – found that lawsuits over laser surgery (e.g., hair removal, facial rejuvenation) are increasing, and doctors have been held liable even if they were not personally operating the device. The researchers found that from 1985 to 2012 there has been a gradual increase in litigation and verdicts, with a peak in 2010.

- The largest number of cases was in California, New York, and Texas.
- Plastic surgeons were sued the most often (26% of cases), followed by dermatologists (21%).
- Non-physicians (e.g., nurses and aestheticians) were the laser operators in ~40% of cases.
- Procedures/conditions most commonly involved in litigation were: hair removal (36%), skin rejuvenation (25%), vascular lesions (8%), and leg veins (8%).
- In cases where the final disposition was known, defendants won 49% of the time, plaintiffs won 27% of the time, and 24% were settled out of court.

Plastic surgery – annual report

The American Society of Plastic Surgeons' annual report on procedures performed in the U.S. found that in 2012:

- More than 14.6 million procedures were performed, up 5% from 2011.
- Surgeries declined 2%.
- Minimally-invasive cosmetic treatments increased 6%.
- Breast augmentation remained the No. 1 cosmetic surgery, with >286,000 implants performed, but surgical volume declined 7% vs. 2011.
- Buttocks augmentation declined 36% vs. 2011 to <3,800 procedures.
- Botulinum toxin injections were the most commonly performed cosmetic procedures, with 6.1 million procedures performed, up 8% vs. 2011.
- Facial filler patients increased 5% to nearly 2 million people.
- Nearly 2.2 million laser or intense pulse light (IPL) treatments were performed, a 6% increase over 2011.
- Facelifts were up 6%, eyelid lifts up 4%, and cheek implants up 6%.

TORAX MEDICAL's LINX Reflux Management System – positive results preventing GERD

In a 100-patient study published in the ***New England Journal of Medicine***, 64% of patients who got this device – a ring of tiny magnetic beads that are surgically placed around the lower esophageal sphincter to prevent gastroesophageal reflux disease (GERD) – met the primary endpoint (normalized acid exposure in the esophagus or a reduction in acid exposure of ≥50% after 1 year). The researchers also reported that >90% of patients met key secondary endpoints, including a reduction of ≥50% in the use of proton pump inhibitors (PPIs), as well as improvement of ≥50% in quality-of-life scores relative to baseline when not taking a PPI.

REGULATORY NEWS

FDA still mulling hydrocodone scheduling

The FDA hasn't made a decision on whether to recommend the Drug Enforcement Administration (DEA) move hydrocodone from Schedule III to the more restrictive Schedule II, but a bipartisan group of senators and representatives sent a letter to the Agency urging the FDA to act or **at least say when it will** act. They wrote, "The American people have waited too long for action from this agency."

The letter was signed by two Republicans (Rep. Mark Kirk of Illinois and Rep. Vern Buchanan of Florida) as well as five Democrats: Rep. Edward Markey (MA), Sen. Joe Manchin (WV), Sen. John Rockefeller (WV), Sen. Charles Schumer (NY), and Sen. Kirsten Gillibrand (NY).

OIG says Medicare overpaying for infusion drugs

The Department of Health and Human Services' Office of the Inspector General (OIG) said its investigation found that Medicare (Part B) is overpaying for infused drugs because it uses the average wholesale price set by manufacturers and reported in the industry's Red Book. The OIG estimated that using this payment method results in a cost 54%-122% above the market price. The OIG estimated that Medicare would pay 44% less if it used the average sales price.

FDA wants pediatric data on devices

The FDA issued a supplemental proposal mandating that medical device companies include data on pediatric patients when applying for premarket approval (PMA), a PMA supplement, a humanitarian device exemption request, or a product development protocol. Comments on this proposal will be accepted through April 22, 2013.

FDA approvals/clearances

- AGILENT TECHNOLOGIES/DAKO's HER2 IQFISH pharmDx, a rapid test for identifying the HER2 gene in breast cancer patients, was cleared for use.
- ALLERGAN's Natrelle 410, an anatomically shaped silicone gel-filled breast implant, was approved. The FDA mandated a series of post-approval studies to assess long-term safety and effectiveness and the risk of rare disease. The FDA is requiring the company to:
  - Follow ~3,500 women for an additional five years.
  - Conduct a 10-year study of >2,000 Natrelle 410 patients to collect information on long-term local complications (e.g., capsular contracture, removal of implant, reoperation, implant rupture) and less common potential disease outcomes (e.g., rheumatoid arthritis, breast and lung cancer, reproductive complications).
  - Conduct five case control studies to evaluate the possible association between the Natrelle 410 implants, as well as other silicone gel-filled breast implants, and five rare diseases – rare connective tissue disease, neurological disease, brain cancer, cervical/vulvar cancer, and lymphoma.
  - Evaluate women's perceptions of the patient labeling.
  - Analyze the Natrelle 410 implants that are removed from patients and returned to the manufacturer.

- **LOMBARD MEDICAL TECHNOLOGIES' Aorfix** stent was cleared to treat abdominal aortic aneurysm in patients with up to 90 degrees of angulation at the neck of the aneurysm.
- **NOVARTIS' Zortress (everolimus)** received expanded approval to prevent liver transplant rejection in adults as well as kidney transplant rejection.
- **OXFORD PERFORMANCE MATERIALS' OsteoFab system**, an implantable device that is tailored to each patient to help replace skull voids caused by disease or trauma, received 510(k) clearance.
- **ROCHE/GENENTECH and IMMUNOGEN's Kadcyla (ado-trastuzumab emtansine, T-DM1)** was granted accelerated approval to treat women with HER2-positive metastatic breast cancer who were previously treated with Herceptin (trastuzumab) and taxanes. The drug will have a boxed warning to alert patients and doctors that it can cause liver toxicity, cardiac toxicity, and death. The FDA also advises that pregnancy status be verified prior to starting Kadcyla because the drug can cause severe birth defects.
- **SANITAS' Wellaho** mobile technology platform, a personalized outpatient management device designed to help chronically ill patients keep track of their conditions and to let doctors monitor them and oversee treatment between office visits, was approved as a Class II medical device.

FDA recalls/warnings

- **AFFYMAX and TAKEDA's Omontys (peginesatide)** – The companies voluntarily pulled this once-monthly anemia drug used for dialysis patients – a competitor to Amgen's Epogen (epoetin alfa) – from the U.S. market because of ~50 reports of serious hypersensitivity reactions (a rate of ~0.02%) and at least five deaths. The FDA said it had received 19 reports of anaphylaxis from dialysis centers and knew of three deaths. The company urged healthcare providers to stop using Omontys immediately.

  The FDA approved Omontys in March 2012, after the Oncologic Drugs Advisory Committee voted 15-1 in December 2011 to recommend approval. The panel had some concerns about cardiovascular safety, but anaphylaxis and hypersensitivity reactions never came up at that meeting.
- **ALCON LENSX's LenSx Laser System** – The FDA sent Alcon LenSx a warning letter saying that the company did not show that it is working to correct deficiencies at its plant, including oscillator problems in at least 10 LenSx laser systems that failed during in-house final testing and 12 LenSx laser systems that experienced out-of-box failures between September 2011 and April 2012. The FDA also told the company that it did not report some significant software updates for which a new 510(k) is required.
- **GILEAD SCIENCES' Vistide (cidofovir for intravenous infusion)** – One lot of this treatment for cytomegalovirus (CMV) retinitis in patients with AIDS was recalled because some vials contain an unknown particulate.
- **JOHNSON & JOHNSON/DEPUY's LPS Diaphyseal Sleeve** – A Class I recall was initiated because the taper connection for the LPS knee implant may not be strong enough to handle the load during walking, leading to fracture, loss of function, infection, or even loss of limb. The FDA has received 10 reports of malfunctions (6 fractures and 4 loosenings).
- **SOLTA MEDICAL's Isis laser, Serenity skin rejuvenation system, and Janus resurfacing laser** – The FDA sent the company a warning letter about what it called "objectionable conditions" observed in three clinical trials of the devices, including failure to include all appropriate elements of informed consent, failure to give investigators information to conduct the trial properly, failure to ensure proper monitoring, failure to obtain signed investigator agreements, insufficient accurate financial disclosure information, and failure to maintain accurate, complete, and current device shipment and disposition records.

European regulatory news

- **APIFIX's adolescent scoliosis correction device** received a CE Mark.
- **BIOTRONIK's Ilesto 7 implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy defibrillators (CRT-Ds)** received a CE Mark.
- **BONESUPPORT's Cerament G**, an injectable ceramic bone replacement system designed to promote bone healing while preventing infection, received a CE Mark.
- **NXSTAGE MEDICAL's System One**, a noctural in-home hemodialysis system, received a CE Mark. The company plans to launch it in 2H13.
- **OSIRIS THERAPEUTICS' prochymal**, a stem cell treatment for acute graft-versus-host disease in bone marrow transplant patients, received orphan drug status from the EMA.
- **VIVUS' Qsiva (phentermine + topiramate)** – For the second time, the EMA's Committee for Medicinal Products for Human Use (CHMP) recommended against approving this obesity drug (sold as Qsymia in the U.S.), saying it is concerned about "the long-term effects on the heart and nervous system." CHMP wants the company to conduct a cardiovascular outcomes trial.

Regulatory news from other countries

Japan: **ACTELION PHARMACEUTICALS' ACT (epoprostenol) –** The Japanese Ministry of Health, Labor, and Welfare approved this pulmonary arterial hypertension (PAH) drug (which is marketed in the U.S. as Veletri).

2013 FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
February 25	Discussion of FDA regulation of new drugs to treat **amyotrophic lateral sclerosis** (ALS)	FDA public hearing
February 26	**QuatRx Pharmaceuticals** and **Shionogi's ospemifene**, a SERM for painful intercourse in women	PDUFA date
February 28	**Lundbeck** and **Otsuka's aripiprazole depot** to treat schizophrenia	PDUFA date
March 1	**Zogenix's Zohydro** (extended-release hydrocodone) for chronic pain	PDUFA date
March 4	**Depomed's gabapentin** and **Noven Therapeutics' paroxetine** – both to treat moderate-to-severe vasomotor symptoms of menopause	FDA's Reproductive Health Drugs Advisory Committee
March 5	Efficacy vs. cancer risk with calcitonin-salmon products **– Novartis' Miacalcin** (calcitonin-salmon – injection and nasal spray) and **Upsher-Smith Laboratories' Fortical** (calcitonin-salmon recombinant nasal spray) – for the treatment of postmenopausal osteoporosis	Joint meeting of the FDA's Reproductive Health Drugs Advisory Committee and the FDA's Drug Safety and Risk Management Advisory Committee
March 7	**GlaxoSmithKline's Breo Ellipta** (fluticasone furoate + vilanterol), a dry powder inhaler for chronic obstructive pulmonary disease (COPD)	FDA's Pulmonary-Allergy Drugs Advisory Committee
March 14	Discussion of the FDA's **draft risk assessment model** for potential exposure to the variant **Creutzfeldt-Jakob disease (vCJD) agent in red blood cells for transfusion** in the U.S.	FDA's Transmissible Spongiform Encephalopathies Advisory Committee
March 17	**Bristol-Myers Squibb** and **Pfizer's Eliquis** (apixaban,) an oral anticoagulant to prevent stroke in atrial fibrillation patients	PDUFA date
March 18	**Pharmaxis' Bronchitol** (mannitol) for cystic fibrosis	PDUFA date
March 20	**Abbott's MitraClip** for mitral valve repair	FDA's Circulatory System Devices Advisory Committee
March 22	**Cangene's BAT** (botulinum antitoxin), an anti-bioterrorism agent	PDUFA date
March 28	**Biogen Idec's BG-12** (dimethyl fumarate) for multiple sclerosis	PDUFA date (extended from December 28, 2012)
March 31	**Johnson & Johnson's Invokana** (canagliflozin), a SGLT2 inhibitor to treat Type 2 diabetes	PDUFA date
April 11	Potential effects of extreme weather and natural disasters on **medical device safety and quality**	FDA's Device Good Manufacturing Practice Advisory Committee
April 15	**MAP Pharmaceuticals' Levadex** (dihydroergotamine), inhaled migraine drug	PDUFA date
April 29	**Shire's Vyvanse** (lisdexamfetamine dimesylate), sNDA for ADHD treatment in children	PDUFA date
April 29-30	Discussion of **medical device labeling standardization**, including an online labeling repository for in-home medical devices	FDA public workshop
April 30	**Raptor Pharmaceutical's Procysbi** (cysteamine bitartrate delayed-release, RP-103) to treat nephropathic cystinosis	PDUFA date (extended from January 30, 2013)
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	**PET imaging** of brain beta-amyloid	CMS coverage decision expected
July 28	**Aveo Oncology** and **Astellas Pharma's Tivopath** (tivozanib) to treat advanced renal cell carcinoma	PDUFA date
August 17	**ViiV Healthcare's dolutegravir** for HIV	PDUFA date
October 2	**Lundbeck** and **Takeda's Brintellix** (vortioxetine), an antidepressant for major depressive disorder	PDUFA date
October 3	**Pfizer** and **Ligand Pharmaceuticals' Aprela** (bazedoxifene/conjugated estrogens) to treat menopausal symptoms and osteoporosis prevention	PDUFA date
October 19	**Actelion's Opsumit** (macitentan), a dual endothelin receptor antagonist to treat pulmonary arterial hypertension	PDUFA date
December 18	**GlaxoSmithKline** and **Theravance's Anoro** (umeclidinium bromide + vilanterol) for COPD	PDUFA date