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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SHORT TAKES

- **ABLYNX** formed a research collaboration with **Algeta** to explore the combination of nanobodies with thorium-227 using Algeta's proprietary Targeted Thorium Conjugate (TTC) technology.

- **ARIAD PHARMACEUTICALS' ponatinib –** A 65-patient Phase I study published in the ***New England Journal of Medicine*** suggested that this once-daily, oral tyrosine kinase inhibitor (TKI) shows promise in treating Philadelphia chromosome-positive chronic myeloid leukemia (CML) patients. In the study, 98% of the 43 patients with chronic-phase CML had a complete hematologic response, 72% had a major cytogenetic response, and 44% had a major molecular response. Of the eight patients with a T315I mutation, 100% had a complete hematologic response, and 92% had a major cytogenetic response.

- **Aromatase inhibitors –** A study published in ***Cancer*** suggests that direct-to-consumer (DTC) advertising for aromatase inhibitors leads to more prescriptions being written for the drugs but ***not*** an increase in inappropriate use.

- **ASTRAZENECA's selumetinib –** A study published in ***The Lancet Oncology*** found that adding this investigational drug to standard chemotherapy (docetaxel) decreased tumor size and prolonged disease-free survival (DFS) vs. docetaxel alone in non-small cell lung cancer patients with a KRAS mutation. The combination appeared synergistic.

- **BAYER and ONYX's Stivarga (regorafenib, BAY-73-4506) –** A study published in ***The Lancet*** found that progression-free survival (PFS) was 4.8 months with regorafenib vs. 0.9 months with placebo, regardless of the number of prior courses of therapy. Stivarga is currently under review by the FDA and the European Medicines Agency (EMA) as a third-line treatment for gastrointestinal stromal tumors (GIST).

- **CYTOKINETICS' tirasemtiv (CK-2017357) –** The company said a 32-patient Phase IIa trial of this oral neuromuscular drug showed promise in myasthenia gravis, with patients having statistically significant improvements in a disease scoring system and in the amount of air they could expel from their lungs six hours after dosing.

- **DUNE MEDICAL DEVICES' MarginProbe System –** The company said the FDA told the company that it will approve Dune's premarket approval application (PMA) for this breast cancer detection device during surgeries once there is agreement on the design of the required postmarketing study.

- **FOREST LABORATORIES and GEDEON RICHTER's cariprazine (RGH-188)** – Forest said it submitted a new drug application for this antipsychotic to treat schizophrenia and for manic or mixed episodes associated with bipolar I disorder. Forest is hoping to launch the drug in 1H14.

- **GE HEALTHCARE** introduced a magnetic resonance imaging (MRI) system that is much quieter than the typical MRI, which is very noisy, which should make patients a little happier about the test.

- **GILEAD SCIENCES' sofosbuvir (GS-7977)** – The company said that 78% of the patients given this once-daily NS5B nucleotide inhibitor + ribavirin in the 207-patient Phase III POSITRON trial had undetectable levels of virus at Week 12 vs. no placebo patients.

- **GIVEN IMAGING's PillCam Colon 2 endoscopic capsule** was submitted to the FDA for approval to image the lower gastrointestinal tract.

- **GLAXOSMITHKLINE's Avodart (dutasteride)** – A 294-patient, 24-month study published in the journal ***European Urology*** found that this treatment for benign prostatic hyperplasia (BPH) also delays the clinical progression of prostate cancer in patients with elevated PSA levels post-radical prostatectomy. At the end of the study, patients on 0.5 mg dutasteride had a significant 66% reduction in PSA doubling time vs. placebo.

- **LILLY's Cialis (tadalafil)** – A study published in the journal ***Science Translational Medicine*** found that this erectile dysfunction drug may improve blood flow and slow disease progression in patients with Becker muscular dystrophy (BMD). Researchers at Cedars-Sinai Heart Institute in Los Angeles used infrared imaging technology to study 10 patients given a single 20 mg dose of Cialis and found that 8 of the patients had a significant improvement in blood flow in their forearm muscles vs. placebo.

- **Lindane** – The FDA rejected a request to ban the use of this insecticide in shampoos to treat head lice, saying "the current labeling adequately addresses benefits and risks" and pointing out that there is "no new evidence to question effectiveness," which the FDA said is ~96%.

- **MEDTRONIC** – A study reported in the ***Journal of the American College of Cardiology*** found that opening the internal pudendal artery (IPA) with a zotarolimus-eluting stent may be effective in treating atherosclerotic erectile dysfunction (ED) in men who don't respond to PDE-5 inhibitors.

- **MERCK's suvorexant** – A crossover study in 254 healthy volunteers – published in ***Neurology*** – suggests that this orexin inhibitor may be a useful treatment for insomnia. It works differently from other insomnia drugs. In the study subjects who took suvorexant had more total sleep time and less awake time in the middle of the night than placebo patients. Suvorexant was generally well tolerated, with no serious side effects. It has been submitted to the FDA.

- **OXIGENE's OXi-4503,** an investigational drug for acute myelogenous leukemia (AML), was granted orphan drug status by the FDA.

- **PFIZER's Torisel (temsirolimus)** – A retrospective pilot study published in the ***International Journal of Clinical Oncology*** found that this mTOR inhibitor stabilized disease progression in patients with metastatic renal cell carcinoma (mRCC) undergoing hemodialysis.

- **RANBAXY LABORATORIES' Absorica (isotretinoin)**, a treatment for refractory acne that was in-licensed from **Cipher Pharmaceuticals**, was launched in the U.S.

- **ROCHE's Tamiflu (oseltamivir)** – In response to criticism by researchers at the Nordic Cochrane Centre that there is no evidence that Tamiflu stops or mitigates the flu, Roche is making its clinical trial information available for a multidisciplinary advisory panel to review. Roche said it denied Cochrane's request because the Cochrane team was unwilling to sign a confidentiality agreement.

- **ST. JUDE MEDICAL's Amplatzer** – In a ***CRTonline*** survey, 50% of respondents said they believe that, based on the results of the RESPECT and PC trials, this patent foramen ovale (PFO) closure device should be approved in the U.S. ***only*** in patients who have had two episodes of stroke, while 35% said it should not be approved at all based on those trials, and 15% said it should be approved.

- **SEATTLE GENETICS' Adcetris (brentuximab vedotin)** was granted orphan drug status by the FDA as a treatment for mycosis fungoides, a type of T-cell lymphoma.

- **Simvastatin** – A study published in the ***American Journal of Pathology*** found that topical application of this generic cholesterol drug decreased wound healing time in diabetic mice. *Will it work in humans?*

- **TEVA PHARMACEUTICALS** is delaying its launch of generic versions of two **Gilead Sciences** HIV drugs – **Truvada** (emtricitabine and tenofovir disoproxil fumarate) and **Viread** (tenofovir) – until June 2013 if a judge doesn't rule in its favor by then in the patent case brought by Gilead.

- **THERAVANCE's Vibativ (telavancin)** – The FDA's Anti-Infective Drugs Advisory Committee voted 9-6 against recommending approval of a new indication for telavancin to treat hospital-acquired pneumonia because of concerns over renal toxicity. However, the panel also voted 13-2 that it is effective in treating nosocomial pneumonia patients with no other options. Many panel members felt it could be approved for a very narrow indication – nosocomial pneumonia patients with methicillin-resistant *Staphylococcus aureus* (MRSA) with creatinine clearance >30 mL/min.

NEWS IN BRIEF

ARQULE and DAIICHI SANKYO's tivantinib (ARQ-197) – effective second-line for high-MET HCC patients

A 107-patient Phase II study published in ***The Lancet Oncology*** found this MET inhibitor is an effective second-line therapy for patients with unresectable hepatocellular carcinoma (HCC) whose tumors exhibit high-MET expression. Overall, time-to-progression (TTP) was 1.6 months with tivantinib vs. 1.4 months with placebo, but there was no significant difference in overall survival (6.6 months vs. 6.2 months).

However, the study found that expression of the MET proto-oncogene is an independent prognostic factor in patients who have failed to respond to first-line treatment and could be used to select patients who are most likely to benefit from treatment. In patients with high-MET tumors, tivantinib significantly increased median TTP – 2.7 months vs. 1.4 months with placebo. In these patients, median survival was improved (7.2 months vs. 3.7 months).

In patients with low-MET tumors, there was no difference in efficacy with tivantinib vs. placebo.

BRISTOL-MYERS SQUIBB's avagacestat (BMS-708163) – is the γ-secretase class dead in AD?

A 209-patient, 6-month, Phase II study published in the ***Archives of Neurology*** details how patients with mild-to-moderate Alzheimer's disease who took this oral γ-secretase inhibitor had more adverse events (GI, skin, etc.) and, at the highest dose, ***poorer*** cognition than placebo patients. The findings were reported in July 2011 at the 2011 Alzheimer's Association International Conference in Paris, but this is the first detailed publication of the data, and experts said the findings are a red flag for γ-secretase inhibitors in general.

A Phase II trial of avagacestat in prodromal AD is still ongoing, but an interim analysis will be complete by the end of 2012.

Diet drugs – three pieces of news

- **Diet drink.** Oxford University researchers have developed a new drink, dubbed DeltaG, that not only helps people lose weight but also may treat epilepsy, diabetes, and Alzheimer's disease – and boost energy. The discovery was made by Kieran Clarke, PhD, a biochemist, and was funded by DARPA (the U.S. Defense Advanced Research Projects Agency).

  What's the magic ingredient? Ketones. Ketones are the reason why high-fat diets such as the Atkins diet work.

  In rats, the drink boosted physical and mental performance – and the rats became healthier, losing body fat and getting lower triglyceride and glucose levels – with no adverse events. In the first human study, patients lost weight, glucose levels fell, and cholesterol levels fell.

- **AMGEN's mimAb1.** According to a study published in ***Science Translational Medicine***, this engineered antibody inactivates the FGF21 pathway, causing significant weight loss in obese monkeys. After just two injections, given two weeks apart, the monkeys lost 10% of their body weight (without reducing caloric intake), and the weight loss was maintained out to 9 weeks after the second injection. Insulin sensitivity, abdominal circumference, and body mass index (BMI) all decreased.

- **AETNA** issued a clinical policy bulletin on obesity drugs, for use by indemnity plans that choose to cover these drugs as part of their ***medical*** coverage. An Aetna official said that currently only a small minority of plans cover obesity as a medical benefit (separate from a pharmacy benefit), "In this case there are some indemnity plans that include obesity coverage, but the way it is structured, it has to be under a medical benefit. So, this update was for that."

  It is unlikely that the new policy will encourage many more plans to add these drugs as a ***medical*** benefit. The Aetna official said, "Our clinical policies don't dictate plan coverage."

  The seven drugs listed in the policy bulletin are:
  - Arena Pharmaceuticals and Eisai's Belviq (lorcaserin)
  - Roche's Xenical (prescription orlistat)
  - GlaxoSmithKline's Alli (orlistat over-the-counter)
  - Valeant Pharmaceuticals' Bontril (phendimetrazine)
  - Phentermine
  - Vivus' Qsymia (phentermine + topiramate)
  - Watson Laboratories and CorePharma's generic Tenuate (diethylpropion)

Asked why Aetna issued the new policy now, the official said, "With any new treatment, it happens when the evidence and the science behind the drugs start to show results…When our doctors look at clinical policy, they look at evidence, peer reviewed literature, recommendations from medical organizations, etc. Is there enough clinical evidence these drugs are effective for this condition? And if the science supports it, they consider it medically necessary to cover them. But that doesn't necessarily make it a part of a covered benefit plan…For plans that want to include [obesity drugs], we want to be sure we have all the facts… and if they do want to do it, that we have looked at what is safe and effective."

As with medical plans, few ***pharmacy*** plans cover obesity drugs right now. Aetna is planning to issue another clinical policy soon for obesity drugs for ***pharmacy*** plans, and the Aetna official said it is likely to have the same drug decisions as in the clinical policy for medical plans. Then, for plans that decide to include obesity drugs, how they are paid would be determined by the plan's formulary. That is, generic obesity drugs may be in one tier, and higher priced brand drugs could be in higher tiers. The tier would be decided by the type of drug, not be specific to obesity drugs.

Digoxin – tied to rise in deaths among AFib patients

A study published in the ***European Heart Journal*** found that this cardiac rhythm drug was linked to a significant increase in deaths in atrial fibrillation (AFib) patients. It is well known that digoxin has a narrow therapeutic window, but researchers from the University of Kentucky found that AFib patients in the 4,060-patient AFFIRM trial who took digoxin had a 41% increase in all-cause death, even after controlling for other medications and risk factors. The increased mortality occurred regardless of gender or the presence/absence of underlying heart failure.

In the study, digoxin was associated with a 35% increase in cardiovascular death and a 61% increase in arrhythmia deaths. The researchers concluded, "These results mean that among AFib patients taking digoxin compared to those not on digoxin …within five years one additional patient out of six will die from any cause, one additional patient out of eight will die from cardiovascular causes, and one additional patient out of 16 will die from arrhythmias…These findings call into question the widespread use of digoxin in patients with AFib, particularly when used for controlling AFib rate in a similar way as in the AFFIRM trial."

The mechanism by which digoxin increases mortality is not known.

e-prescribing – becoming *the* thing to do

Almost half of the doctors in the U.S. (48%) are doing e-prescribing using an electronic health record (EHR), and that's up from 7% in 2008. The Office of the National Coordinator for Health Information Technology (ONC) said the increase is due to (1) increased pharmacy participation and (2) Medicare meaningful use incentives for physicians.

- The states with the highest growth in e-prescribing over the past four years were Iowa, Minnesota, New Hampshire, North Dakota, and Wisconsin.
- >88% of community pharmacies in every state are enabled to accept e-prescriptions vs. 76% in 2008.

Gastric bypass – no long-term benefit in diabetes

A study published in ***Obesity Surgery*** suggests gastric bypass may not be as beneficial for treating Type 2 diabetes as originally thought. The study looked at 4,434 adult diabetics from three large health plans in California and Minnesota who had Roux-en-Y gastric bypass and tracked them over 13 years (1995-2008) and found:

- 68% of bypass patients had complete remission of their Type 2 diabetes.
- Within five years, 35% of those whose diabetes resolved developed diabetes again (relapsed).
- 56% of patients overall had no long-lasting remission of their diabetes after surgery.
- Weight regain – while common after bariatric surgery – did not appear to be the cause of the return of the Type 2 diabetes. The patients most likely to relapse were those who had been diabetic for a long time, had poor glucose control, or were taking insulin.

HEALTH MANAGEMENT ASSOCIATES (HMA) – under investigation and subject of 60 Minutes exposé

CBS' 60 Minutes aired a negative story on December 2, 2012, about hospital admissions from HMA's emergency rooms, suggesting that medically unnecessary inpatient admissions were being made. HMA was subpoenaed in 2011 by the Office of the Inspector General, and that investigation (likely a Medicare False Claims action) is still ongoing.

60 Minutes talked to more than 100 current and former employees, who charged that the company (at the highest levels) "relentlessly pressured doctors to admit more and more patients, regardless of medical need, to increase revenue."

Some of the former employees – including emergency room doctors – claim they were threatened with the loss of their job (and some claim they did lose their job) for not meeting admission goals. One former employee called it "coercion to commit fraud."

A former FBI agent who conducted an audit for HMA said he reported what he found and lost his job for his frankness. His opinion: "It was Medicare fraud. Simple as that. They are submitting bills to the government for hundreds of thousands of dollars in inappropriate hospital stays."

The former staffers/doctors said HMA's goal was admitting 20% of all patients seen in the ER and 50% of all Medicare-age patients.

However, the company insisted that its admission rates are comparable to national averages and local competitors. If there is an excess of admissions, the company said it was due to third-party software from **ProMed Clinical Systems**, which HMA has ceased using, but ProMed officials denied that their software could be the culprit.

Hepatitis C screening – value questioned

Three studies intended to help the U.S. Preventive Services Task Force decide what to recommend about screening for hepatitis C virus reported mixed results. The studies, which were published in the ***Annals of Internal Medicine***, found:

- No direct evidence that screening asymptomatic people improves clinical outcomes.
- No published evidence on long-term effectiveness of treatment.
- No interventions that reduce the risk of mother-to-child transmission of the virus.
- SVR is associated with a lower risk of poor outcomes and perhaps lower all-cause mortality.

Hospital safety scores – controversial

While 790 hospitals got an A grade in Leapfrog Group's annual Hospital Safety Score, some big name hospitals failed or nearly failed. For example, Ronald Reagan UCLA Medical Center in Los Angeles got an F, and the Cleveland Clinic's score was a D.

The grades, which are based on 26 voluntarily reported measures, reflect the risk that a patient will suffer a preventable medical error, an injury, an accident, or an infection while hospitalized. A Leapfrog official said the D and F grades "represent the most hazardous environments for patients in need of care."

In an interview with ***HealthLeaders Media***, a Leapfrog official said most low-scoring hospitals realize they have a patient safety problem but not how serious that problem is.

However, the scores are controversial. UCLA, denying its hospital deserves an F, criticized the Leapfrog methodology. The American Hospital Association said the scores were inaccurate and advised patients not to use them to make decisions about where to receive care.

JOHNSON & JOHNSON

- **Sirturo (bedaquiline).** The FDA's Anti-Infective Drugs Advisory Committee recommended accelerated approval of this adenosine triphosphate synthase enzyme inhibitor to treat multi-drug resistant pulmonary tuberculosis as an adjuvant to standard TB treatments, based on two Phase II trials. The panel voted 18-0 that it is effective and 11-7 that it is safe. The safety concern was elevated liver enzymes and QT prolongation in some patients. The PDUFA date is December 29, 2012.
- **Stelara (ustekinumab).** A mouse study published in the journal ***Nature Medicine*** found that this psoriasis therapy may slow the accumulation of beta-amyloid plaques in the brain, suggesting it may be a useful therapy in Alzheimer's disease. In older mice with established disease, ustekinumab treatment results in a marked improvement in cognitive function. However, experts cautioned that this is very early preclinical research.

SECOND SIGHT MEDICAL PRODUCTS' Argus II Retinal Prosthesis System – lets blind read some braille images

A study published in the journal ***Frontiers in Neuroprosthetics*** found that a blind patient was able to read Braille patterns that were streamed directly onto the retina using this device. The patient could read words with up to four letters accurately and quickly.

In September 2012, the FDA's Ophthalmic Devices Panel of the Medical Devices Advisory Committee voted unanimously (19-0) to recommend approval of this device, which includes a video camera attached to a pair of eyeglasses, a processing unit, and an implanted retinal prosthesis. The eyeglasses capture images, which are sent to a processing unit worn on a belt. The processor transforms the images into an electrical stimulation pattern that is transmitted to the implanted retinal prosthesis.

REGULATORY NEWS

CMS oversight of EHR incentive payments criticized

The Department of Health and Human Services' Office of the Inspector General (OIG) strongly criticized the Centers for Medicare and Medicaid Services (CMS) for not being sure that the payments it is making for use of electronic health records (EHRs) under the "meaningful use" incentive program are going to doctors and hospitals that really earned them. As of September 2012, CMS had paid ~$4 billion in incentives to 82,535 professionals and more than 1,400 hospitals, according to the OIG.

The OIG said CMS does not have strong pre-payment safeguards to be sure that providers actually meet the requirements for the incentives. Providers self-report EHR usage online, and there is little CMS oversight before the payments are made.

CMS is supposed to audit selected physicians and hospitals after payment to assure self-reported meaningful use information is correct, but at the time of the OIG's audit, CMS had not completed any post-payment audits. Even if CMS did audit a provider, the OIG found that CMS can't verify all self-reported information because it doesn't require the technology to be capable of producing reports for all meaningful use measures. And reports from EHRs could produce inaccurate information.

Furthermore, the OIG found that if there is an on-site audit, providers may not have all the data needed to verify self-reported information, and CMS hasn't provided guidance on what is needed to support documentation. The OIG itself is conducting audits of Medicare and Medicaid EHR incentive payments.

CMS Administrator Marilyn Tavenner told the OIG that her agency is in the process of implementing a batch reporting mechanism that will enable a provider to submit a batch file of attestation information generated by the EHRs for all of a group's individual eligible professionals. She said this should "further enhance the accuracy of the data submitted by providers."

FDA improves device review times

An FDA report said ~80% of medical devices submitted through the 510(k) pathway were approved in 2012 vs. 73% in 2010. The average review time also dropped. The FDA credited better submissions from manufacturers.

FDA seeks comment on medical device review rules

The FDA has proposed new protocols for custom medical device reviews, and the Agency is seeking public comments and information on – and examples of – appropriate use of the custom medical exemption system, including input from patients, manufacturers, dentists, and physicians on situations in which they have used or would like to use custom devices.

Who should regulate bed rails – FDA or CPSC?

The Consumer Product Safety Commission (CPSC) estimates that at least 37,000 people were injured and 155 adults (mostly elderly) died between 2003 and 2012 after becoming trapped in bed rails, and ~4,000 adults were treated annually in emergency departments for bed rail injuries. Both the FDA and the CPSC agree the real numbers are probably much higher.

The FDA issued a safety warning about bed rails in 1995 and instituted "voluntary guidelines" in 2006. Experts believe more warnings are needed, but who should regulate them – the FDA or CPSC? Bed rails that don't have medical claims are considered by the FDA as consumer safety devices, but the CPSC maintains that bed rails are medical devices.

Rep. Edward Markey (D-MA) called for the CPSC, the FDA, and the Federal Trade Commission (FTC) to form a task force to address the regulation of bed rails and bed systems, specifically rails that blur the line between being medical devices and consumer products.

So, bed rail manufacturers should expect new rules.

FDA approvals/clearances

- **EXELIXIS' Cometriq (cabozantinib)** was approved to treat metastatic medullary thyroid cancer, which affects ~2,250 Americans annually. The drug has a boxed warning about the possibility of severe and fatal bleeding and perforations of the colon.
- **GE HEALTHCARE's FlightPlan for Liver**, a 3D imaging tool to help plan liver embolization procedures, was cleared for use.

FDA recalls/warnings

- **BRACCO DIAGNOSTICS' Isovue (iopamidol injection) Pre-Filled Power Injector Syringes** – The company voluntarily initiated a Class I recall of nine lots due to visible particles in syringes observed at the end of standard stability studies on retained samples.

- **INCONTROL MEDICAL's InTone**, a non-implanted electrical stimulator for treating female urinary incontinence – The FDA sent the company a warning letter that its manufacturing is not in conformity with current good manufacturing practice (cGMP) requirements.
- **MINDRAY MEDICAL's A3 and A5 Anesthesia Delivery System** – The company upped this to a Class I recall of the devices due to a gasket leak that could cause an interruption of (or inadequate) patient anesthesia and ventilation, temporary or permanent patient injury, or death. The gasket leak also could cause injury to bystanders and operating room personnel due to exposure to leaking anesthesia gases. Mindray is replacing canister gaskets on affected devices and said ~70% had been corrected as of mid-November.
- **NEXERA MEDICAL's SpectraShield 9500 Surgical N95 Respirator** – The FDA sent the company a warning letter that its production is not in conformity with cGMP requirements.
- **RANBAXY LABORATORIES' generic atorvastatin** – First, the company initiated a voluntary recall of 41 batches of this cholesterol-lowering drug (the 10 mg, 20 mg, and 40 mg doses only, not the 80 mg dose) after some lots were found to contain tiny glass particles. Then, the company said it was halting all production of generic atorvastatin until this issue is resolved.

  Ranbaxy is the largest supplier of generic atorvastatin in the U.S. and was already under close scrutiny by the FDA for a series of quality problems at its plants that even led to a short-term bar on imports to the U.S. Ranbaxy has been operating since December 2011 under a consent decree that requires it to improve its manufacturing procedures.
- **VERATHON's GlideScope GVL Video Laryngoscopes reusable blades** were voluntarily recalled because they were found to be prone to cracks and/or breaks across the tip of the blade, which potentially could result in pieces of the blade breaking off in a patient's mouth and obstructing the airway or being swallowed.

European regulatory news

- The **European Commission** has a new health commissioner, Tonio Borg, Malta's deputy prime minister and foreign minister. He replaces John Dalli, who resigned amid bribery allegations. Borg will oversee the Commission's regulatory programs involving drugs, medical devices, and other industries through October 31, 2014.
- **ABBOTT's Humira (adalimumab)** received expanded approval from the European Commission to treat patients ages 6 to 17 with severe active Crohn's disease who don't respond to traditional therapy.
- **ASPIREO PHARMACEUTICALS' somatoprim** – The EMA's Committee for Orphan Medicinal Products recommended that this somatostatin analog be granted orphan drug status to treat acromegaly.
- **BAYER and REGENERON PHARMACEUTICALS' Eylea (aflibercept)** was approved by the European Commission to treat wet age-related macular degeneration (AMD).
- **CEQUR's PaQ insulin delivery device** – European regulators have granted this wearable, 3-day insulin pump a CE Mark for use by Type 2 diabetics. A limited European launch is planned for 2013, with a broader launch in 2014.
- **EXELIXIS' Cometriq (cabozantinib)** – The EMA accepted the Marketing Authorization Application (MAA) for this investigational drug to treat progressive, unresectable, locally advanced, or metastatic medullary thyroid cancer (MTC).
- **GILEAD SCIENCES' Viread (tenofovir)** – The European Commission approved this antiviral drug both to treat HIV-infected children and teenagers with hepatitis B.
- **IRONWOOD PHARMACEUTICALS and ALMIRALL's Constella (linaclotide)** was approved by the European Commission to treat moderate-to-severe irritable bowel syndrome with constipation (IBS-C). Almirall plans to launch it in Europe in 1H13. In the U.S., where it is approved as Linzess, Forest Laboratories has the marketing rights.
- **ST. JUDE MEDICAL's Assura line of cardiac rhythm management devices** – including the Fortify Assura ICD, Quadra Assura CRT-D, and Unify Assura CRT-D – received a CE Mark.

Regulatory news from other countries

- ***Australia:*** **SANOFI/GENZYME's Aubagio (teriflunomide)** – The 14 mg oral dose was approved by the Australian Therapeutic Goods Administration to treat patients with relapsing-remitting multiple sclerosis.
- ***Canada:***
  - **SENSUS HEALTHCARE's SRT-100 system** was given approval by Health Canada for use in hospitals and private physician practices to treat patients with non-melanoma skin cancer who don't need surgery.
  - Quebec is eliminating the 15-year-old rule that authorized reimbursement for innovative brand drugs supplied through its drug insurance plans even when generics are available. The government said the action will save

>$175 million/year and increase utilization of generic drugs.

- ***China:*** **ASTRAZENECA's Brilinta (ticagrelor)** was approved to treat acute coronary syndrome patients.
- ***Pakistan:*** A new law was signed that will establish the Drug Regulatory Authority of Pakistan, which will regulate medical devices and pharmaceutical products in that country. All agencies that currently oversee medical devices and pharmaceuticals – e.g., the Federal Drugs Control Administration – will become part of the new agency.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
2012		
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 17	**Amarin's Vascepa** (icosapent ethyl, AMR-101), an omega-3 fatty acid pill	FDA NCE decision expected *(extended from November 16, 2012)*
December 20	**Hemispherx Biopharma's Ampligen** (rintatolimod injection, poly I: poly C12U) to treat chronic fatigue syndrome (CFS)	FDA's Arthritis Advisory Committee
December 21	**Alexza Pharmaceuticals' Adasuve** (loxapine) for agitation associated with schizophrenia or bipolar disorder	PDUFA date
December 29	**Aegerion Pharmaceuticals' lomitapide** to treat homozygous familial hypercholesterolemia	PDUFA date
December 29	**Johnson & Johnson's Sirturo** (bedaquiline) to treat multi-drug resistant tuberculosis	PDUFA date
December 30	**NPS Pharmaceuticals' Gattex** (teduglutide) for short bowel syndrome	PDUFA date
2013		
January 16	**Santarus' Uceris** (budesonide) for ulcerative colitis	PDUFA date (extended from October 16, 2012)
January 17	**NuPathe's Zelrix** (transdermal sumatriptan), a migraine patch	PDUFA date
January 21	**Impax Laboratories' Rytary** (IPX-066) for Parkinson's disease	PDUFA date (extended from October 21, 2012)
January 29	**Boehringer Ingelheim's Striverdi Respimat** (olodaterol) for chronic obstructive pulmonary disease (COPD)	FDA's Pulmonary-Allergy Drugs Advisory Committee
January 29	**Sanofi/Genzyme** and **Isis Pharmaceuticals' Kynamro** (mipomersen) for homozygous familial hypercholesterolemia	PDUFA date
January 30	**Pharmaxis' Bronchitol** (mannitol inhalation powder) for the management of cystic fibrosis	FDA's Pulmonary-Allergy Drugs Advisory Committee
January 30	**Raptor Pharmaceutical's cysteamine bitartrate** delayed-release (RP-103) to treat nephropathic cystinosis	PDUFA date
February 2	**Hemispherx Biopharma's Ampligen** (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 Tivopath** (tivozanib) to treat advanced renal cell carcinoma	PDUFA date