TRENDS-in-MEDICINE

February 26, 2012

by Lynne Peterson

Quick Takes

…Highlights from this week's news relating to drugs and devices in development that are not covered in other *Trends-in-Medicine* reports…

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SHORT TAKES

- **AUXILIUM PHARMACEUTICALS' Xiaflex (collagenase clostridium histolyticum)** – Auxilium and **Actelion** formed a long-term partnership for the development, supply, and commercialization of this injected therapy for Dupuytren's contracture and Peyronie's disease in Canada, Australia, Brazil, and Mexico.
- **BOSTON SCIENTIFIC's Ion and Taxus Liberté** were granted new labeling for treatment of acute myocardial infarction (MI), the first drug-eluting stents to get this label.
- **BRISTOL-MYERS SQUIBB's Abilify (aripiprazole)** – The U.S. Attorney's Office for the Southern District of New York subpoenaed company documents as part of its investigation of the company's marketing practices for this antipsychotic. *That generally means the investigation is serious.*
- **CAN-FITE BIOPHARMA's CF-102** was granted orphan drug status by the FDA to treat hepatocellular carcinoma.
- **CELGENE's Abraxane (nab-paclitaxel)** – A U.K. study found that nab-paclitaxel appears to enhance the activity of gemcitabine in pancreatic cancer. In a mechanistic study, using a laboratory model of metastatic pancreatic ductal adenocarcinoma, U.K. researchers showed nab-paclitaxel is most effective when given first and administration of gemcitabine is delayed (briefly).
- **CHELSEA THERAPEUTICS' Northera (droxidopa)** – The FDA's Cardiovascular and Renal Drugs Advisory Committee voted 7-4 (with 1 abstention) to recommend approval of this drug for neurogenic orthostatic hypotension in patients with primary autonomic failure – which can be associated with Parkinson's disease and multiple system atrophy – dopamine beta-hydroxylase deficiency, and nondiabetic autonomic neuropathy.
- **CVS CAREMARK** – The U.S. Office of the Inspector General (OIG) and the Texas Attorney General have requested information from the company about its prescription drug discount program for uninsured and under-insured people, the Health Savings Pass program. The federal investigation is looking for a False Claims violation.
- **ENANTA PHARMACEUTICALS' EDP-239** – **Novartis** exclusively licensed this small molecule, an NS5A inhibitor for hepatitis C, and other Enanta NS5As in a deal that includes worldwide development, manufacture, and commercialization.
- **GILEAD SCIENCES' Viread (tenofovir)** – A study published in the journal ***AIDS*** looked at 10,841 HIV-positive veterans from 1997 to 2007 and found 4,303 had taken Viread at some point. The users had an 11%-34% increased risk of kidney damage every year, even after they stopped taking the drug.

- **GTx's Capesaris (GTx-758)** – The FDA suspended Phase II clinical trials of this oral LH inhibitor in development for advanced prostate cancer after the company reported an increased risk of blood clots in patients getting 1000 mg. The company plans to meet with the FDA to discuss the outlook for future development.

- **IMPAX LABORATORIES' IPX-066** – The FDA accepted the company's filing for this investigational treatment for Parkinson's disease. The PDUFA date is October 21, 2012.

- **OMEROS' NMUR2** – The company received a $1.04 million grant from the National Institute on Drug Abuse (NIDA) to further develop this non-addictive drug to treat pain by affecting the neuromedin U receptor 2.

- **XENOPORT's Horizant (gabapentin enacarbil)** – **GlaxoSmithKline** sued XenoPort, asking a federal judge to rule that GSK has been living up to its marketing agreement with XenoPort and to preserve GSK's exclusive license to this drug for restless leg syndrome.

NEWS IN BRIEF

BACE-1 inhibitors – possible new downside

Blocking BACE-1 is a promising therapy in Alzheimer's disease because it contributes to amyloid plaque formation in the brain. However, a mouse study published in ***Molecular Neurodegeneration*** reported that blocking BACE-1 may have unintended consequences – disrupting normal axonal development and possibly worsening memory impairment.

The researchers found mice with a genetically engineered deficiency in BACE-1 produced offspring with mistargeted olfactory sensory neuron axons, indicating defective axon guidance. The mouse pups had smaller olfactory bulbs, often with malformed glomeruli and randomly oriented, poorly bundled olfactory sensory neuron axons. The researchers said the findings don't necessarily mean the end of BACE-1 inhibitors, suggesting that a dose might be able to be identified that reduces plaque formation without interfering with axonal development. *But this appears to be a major setback.*

Exelixis' cabozantinib –dual c-MET/VEGF inhibition decreases metastases

A study published in ***Cancer Discovery***, a new journal of the American Association for Cancer Research (AACR), found that dual inhibition of c-MET and VEGF reduced tumor invasion and metastasis in a laboratory model of pancreatic neuroendocrine cancer. The two-phase mouse study found that an anti-VEGF reduced tumor size but increased the cancer's invasiveness and metastasis, but also inhibiting c-MET reduced invasion and metastasis. Three c-MET inhibitors were tested: Pfizer's Xalkori (crizotinib) and PF-04217903, which are pure c-MET inhibitors, and cabozantinib, which targets both VEGF and c-MET.

FOREST LABORATORIES' Tudorza Pressair (aclidinium) – FDA panel recommends approval

The FDA's Pulmonary-Allergy Drugs Advisory Committee voted 12-2 to recommend approval of this BID inhaled powder for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The panel also voted 14-0 that the drug is efficacious and 10-3 (with one abstention) that it is safe for the proposed indication. However, panel members agreed a long-term cardiovascular safety trial is essential. (*See separate* ***Trends-in-Medicine*** *in-depth coverage of this panel.*)

Kidney dialysis – more and longer dialysis improves mortality

Four studies – two with implications for **NxStage Medical**'s **NxStage System One** home hemodialysis system – published in the ***Journal of the American Society of Nephrology*** found that frequent, lengthy dialysis (either daytime or at night) is better for both health and survival in renal failure patients than the standard three-times-a-week dialysis.

- **Study 1 by University of Minnesota researchers.** The risk of all-cause mortality was 13% lower with daily home hemodialysis vs. patients on a conventional three-times-weekly regimen (19.2% vs. 21.7%). In this 1.8 year study of 1,873 NxStage patients vs. 9,365 matched controls, one-year survival was 89.4% with NxStage and 87.4% with the conventional regimen; 80.1% vs. 77.8% at two years.

- **Study 2 by Canadian researchers.** Mortality was 45% less with intensive dialysis (about five 7-hour home dialysis sessions per week) vs. a conventional dialysis regimen. This was a study of 338 NxStage patients vs. 1,388 matched controls. Deaths per 100 person-years was 6.1 with NxStage vs. 10.5 for the conventional regimen.

- **Study 3 by Fresenius Medical Care.** Mortality was reduced by 25% with extended nocturnal dialysis (mean 7.85 hours) vs. conventional dialysis. This was a study of 746 hemodialysis patients vs. 2,062 matched controls.

- **Study 4 by University of Illinois researchers.** Serum phosphorus was significantly reduced when patients got six weekly dialysis sessions, given either during the day or at night.

NOVARTIS' Gilenya (fingolimod) – to be studied in ALS

A Phase IIa/b safety and dose-finding trial is expected to begin in 2012 testing this multiple sclerosis drug in amyotrophic lateral sclerosis (ALS). The hope is that Gilenya will slow the progression of ALS, not cure it. The trial is being organized by the Amyotrophic Lateral Sclerosis Therapy Development Institute (ALS TDI) and will be managed by the Northeast ALS Consortium. Novartis is cooperating but is not an official partner in the study. The principal investigators will be James Berry, MD, and Merit Cudkowicz, MD, both of Massachusetts General Hospital. In terms of the ALS pipeline, this puts Gilenya ahead of **Biogen Idec**'s anti-CD40 antibody, which is also being developed with ALS TDI.

ROCHE's Zelboraf (vemurafenib) – melanoma survival benefit

A study published in the ***New England Journal of Medicine*** reported that this BRAF inhibitor nearly doubled melanoma survival to 16 months in metastatic melanoma patients who hadn't responded to other treatments. The researchers said 53% of patients responded to the drug, 30% had reduction in tumor size, 33% had stable disease, and only 14% of patients didn't benefit.

VIVUS' Qnexa (phentermine/topiramate) – FDA panel recommends approval

The second time around was a winner for this obesity drug. The FDA's Endocrinologic and Metabolic Drugs Advisory Committee, which previously had rejected the drug, voted 20-2 in favor of approval, but the panel urged the FDA to require a postmarketing trial to study the cardiovascular side effects. (*See separate* ***Trends-in-Medicine*** *in-depth coverage of this panel.*)

REGULATORY NEWS

ACIP recommends seniors get Tdap vaccine

The Advisory Committee on Immunization Practices (ACIP) voted to expand its recommendation for the pertussis vaccine (Tdap) to include all people ≥age 65 who haven't had a whooping cough vaccine as an adult. ACIP took the action because of a rebound of pertussis over the last 30 years. Previously, the recommendation was for a single booster dose every 10 years for adults ages 19 to 64 and in people age 65 only if they are likely to come in contact with infants younger than 12 months.

CMS continues initiative to reduced overpayments

The Centers for Medicare & Medicaid Services (CMS) is moving forward with its program to audit Medicare Advantage contracts to reduce the payment error rate in the program. CMS estimates it will recover $370 million in overpayments in the first audit year.

- CMS will perform its next round of Medicare Advantage (MA) contract-level audits on payment year 2011.
- Payment year 2011 is the first year that CMS will conduct payment recovery based on extrapolated estimates.
- CMS expects to audit about 30 MA contracts each year.
- Payment recovery amounts will be subject to a fee-for-service adjuster.

FDA eases shortage of two cancer drugs

The FDA worked out a deal with an Indian company – **Sun Pharma Global** and its authorized distributor, **Caraco Pharmaceutical Laboratories** – to provide Lipodox (liposomal doxorubicin), which is not an FDA-approved drug, to the U.S. temporarily to ease the shortage here of Johnson & Johnson's Doxil and generic Doxil.

The Agency convinced some manufacturers, including **Mylan** and **Sandoz Pharmaceuticals**, to increase their production of methotrexate, easing that shortage as well. In addition, the FDA approved a new manufacturer of a generic, preservative-free methotrexate (**APP Pharmaceuticals**), which should start shipping next month, and that should further bolster supply. In the meantime, **Hospira** also agreed to release additional methotrexate supplies.

Legislation would reduce state inspections

A bill introduced by Rep. Brian Bilbray (R-CA) – the Science and Technology Regulatory Relief Act – would eliminate state inspections of drug and device facilities that duplicate FDA inspections. HR-4056 would amend the Food, Drug, and Cosmetic Act so duplicative state-level inspections would be eliminated, but it would allow state agencies to conduct plant inspections when a drug or device is thought to pose a threat to public safety, when the federal government orders a recall of a product, or if the FDA requests it.

More HHS help for states on ACA implementation

Health and Human Services (HHS) Secretary Kathleen Sebelius said the government is helping states implement three provisions of the Affordable Care Act (ACA) by providing more

resources and more flexibility and transparency:

- Providing a new round of Affordable Insurance Exchange Establishment Grants, totaling $229 million to 10 states – Arkansas, Colorado, Kentucky, Massachusetts, Minnesota, Nevada, New Jersey, New York, Pennsylvania, and Tennessee – to help them build new health insurance marketplaces.
- Promoting transparency and meaningful public input into the Medicaid demonstration process and streamlining the federal-state consideration process as states test new models of care. States will be allowed to undertake experimental, pilot, or demonstration projects that run all or parts of their Medicaid programs in ways that would not otherwise be consistent with federal rules.
- Supporting innovation and implementation of healthcare solutions that work best for the states. This includes a State Innovation Waiver, which will begin in 2017, that will let states pursue their own innovative strategies to ensure their residents have access to high-quality, affordable health insurance.
- Offering more flexibility for states to apply for Exchange Establishment Grants under an amended Funding Opportunity Announcement with additional application opportunities due out later this spring.

FDA briefs

- **Chinese firms linked to heparin contamination barred.** The FDA now has an import alert on 22 Chinese firms that supplied a tainted ingredient during the 2008 heparin crisis.
- **Cooperation critical to user fee program.** FDA Commissioner Margaret Hamburg, MD, told a meeting of the Generic Pharmaceutical Association that the FDA needs the "full cooperation" of drug and device makers to ensure the FDA raises the expected $1.5 billion from user fees over the next five years.
- **Kentucky legislation to boost use of TRF opioids.** House Bill 377, sponsored by Rep. Addia Wuchner, was approved by the Kentucky House Health and Welfare committee by a vote of 13-0. The bill would encourage use of tamper-resistant formulations (TRF) of pain medication in the state as a way to combat prescription-drug abuse.

FDA approvals/clearances

- **ASCENDX SPINE's Acu-Cut Vertebral Augmentation System** was cleared to treat vertebral compression fractures.
- **ELEKTA's Clarity**, an ultrasound device for soft tissue imaging in prostate cancer radiotherapy, was granted 510(k) clearance.
- **ELEKTA's Fraxion**, a system for cranial immobilization for delivery of stereotactic radiation therapy to brain cancer patients, was granted 510(k) clearance.

FDA recalls/warnings

- **AMERICAN REGENT's phenylephrine HCl injection** was recalled due to contamination with visible particles.
- **BEDFORD LABORATORIES** recalled three lots of cytarabine.
- **CAREFUSION's Nicolet Cortical Stimulator Control Unit**, which is used for brain mapping of patients with seizure disorders and brain tumors, was recalled because of two issues which could result in a surgeon resecting the wrong brain tissue, not resecting pathological tissue, or lead to the need for re-operation. Specifically, the device's software can incorrectly indicate stimulation is delivered to an electrode other than the one selected and because a short circuit may develop between units and the stimulus switching unit amplifier.
- **NEMSCHOFF's perinatal bassinets** were recalled because of the risk of injury to patients due to doors and drawers inadvertently opening when the bassinet is in motion.
- **SMITH MEDICAL's Bivona neonatal, pediatric, and Flextend tracheostomy tubes** were recalled because of possible inadvertent dislodgement, which could lead to serious injury or death. This is a Class I recall.

European regulatory actions

- **ABBOTT's Humira (adalimumab)** – The Committee for Medicinal Products for Human Use (CHMP) gave a favorable opinion on this TNF inhibitor to treat moderate-to-severe ulcerative colitis in adults.
- **AMYLIN PHARMACEUTICALS' Byetta (exenatide)** got a positive recommendation from CHMP as add-on therapy for Type 2 diabetes. The European Commission is expected to make a final decision soon.
- **BAYER's Trasylol (aprotinin)** was withdrawn globally in 2007 after a Canadian study linked it to increased mortality, but the European Medicines Agency (EMA) recommended that this drug to prevent excessive bleeding during cardiac surgery be allowed back on the market. CHMP found a number of problems with the way the study that led to the withdrawal was conducted, casting doubt on the previous conclusions. The EMA now believes the benefits outweigh the risks.

- **NOVARTIS' Rasilez/Tekturna (aliskiren)** – The EMA asked the company to update the label for this antihypertensive to warn against use with an ACE inhibitor or ARB in patients with diabetes or kidney problems. Novartis is still discussing this with the FDA.
- **RECOR MEDICAL's Paradise ultrasound renal denervation system** received a CE Mark to treat patients with "resistant" hypertension.
- **ROCHE's Zelboraf (vemurafenib)** was approved by the European Commission as monotherapy of adult patients with BRAF V600, mutation-positive, unresectable or metastatic melanoma.
- **SHIRE's Vpriv (velaglucerase alfa)** – The EMA cleared the company's manufacturing plant in Lexington MA to produce this Gaucher disease drug. Shire is still waiting for FDA approval on production at the plant.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	February 2012	
February 27	The portion of the meeting on appropriate types of evidence for approval of anti-inflammatory drugs for post-op inflammation and pain in patients was canceled, but Topic 2, the portion of the meeting on the appropriateness of marketing a single bottle of **anti-inflammatory ophthalmic products for use in both eyes for post-surgical indications, will still take place as scheduled**, as it relates to the potential risk for infection.	FDA's Dermatologic and Ophthalmic Drugs Advisory Committee
February 28-29	Flu vaccine update, including **Pandemic Influenza Surveillance** and licensure pathways for pandemic flu vaccines	FDA's Vaccines and Related Biological Products Advisory Committee
	March 2012	
March 3	CMS National Coverage Decision on **TAVR** comments	CMS public comment period ends
March 6	**Discovery Labs' Surfaxin** (lucinactant) for infant respiratory disease	PDUFA date
March 6	**Eisai and Astex Pharmaceuticals' Dacogen** (decitabine) to treat acute myeloid leukemia (AML) in older patients	PDUFA date
March 7	**NeurogesX's Qutenza** (transdermal capsaicin) for neuropathic pain	PDUFA date
March 7	Design and methodology for **postmarketing studies**	FDA Public Workshop
March 12	Safety of **anti-nerve growth factor (anti-NGF) drugs** in development to treat a variety of pain conditions. The questions are: Do reports of joint destruction represent a safety signal, and does the risk:benefit balance favor continued development?	FDA's Arthritis Advisory Committee
March 13	**Discussion of appropriate target populations**, objectives, and designs of trials to evaluate drugs to treat hyperbilirubinemia in newborns. In the afternoon, a discussion of development of an unnamed investigational drug	FDA's Gastrointestinal Drugs Advisory Committee
March 20	**GlaxoSmithKline's Votrient** (pazopanib) for advanced soft-tissue sarcoma (in the morning), and **Merck/Ariad's Taltorvic** (ridaforolimus) for maintenance therapy of metastatic soft-tissue sarcoma or bone sarcoma (in the afternoon)	FDA's Oncologic Drugs Advisory Committee (ODAC)
March 21	**Talon Therapeutics' Marqibo** (vincristine sulfate liposomes injection) for Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL)	FDA's Oncologic Drugs Advisory Committee (ODAC)
March 23	Risk:benefit of **Stryker's Wingspan**, a self-expanding nitinol stent already in use under an HDE for treatment of intracranial arterial stenosis	FDA's Neurological Devices Advisory Committee
March 26	**MAP Pharmaceuticals' Levadex** (dihydroergotamine inhalation) for migraine	PDUFA date
March 26-27-28	Oral arguments on the **legality of Obamacare**	U.S. Supreme Court
March 27	**Affymax and Takeda's peginesatide** for anemia	PDUFA date
March 28	**Bristol-Myers Squibb's Eliquis** (apixaban) to prevent strokes in AFib	PDUFA date – delayed but new date not available. Panel May 23.
March 28	**Chelsea Therapeutics' Northera** (droxidopa) for symptomatic neurogenic orthostatic hypotension with primary autonomic failure	PDUFA date
March 28	**Edwards Lifesciences' Sapien** transcatheter aortic valve	CMS expected to publish NCD decision memo
March 28-29	Two-day discussion of pre-and post-approval assessment of **cardiovascular safety for diet drugs and biologics**	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
	April 2012	
April 5	**Astellas' Betanis** (mirabegron), a beta-3-adrenoceptor agonist to treat overactive bladder (OAB)	FDA's Reproductive Health Drugs Advisory Committee
April 17	**Vivus' Qnexa** (phentermine + topiramate) for weight loss	PDUFA date for resubmission
April 25	**Takeda's alogliptin**, a DPP-4 for Type 2 diabetes	PDUFA date
April 25	**HeartWare's HVAD** left ventricular assist device	FDA's Circulatory System Devices Advisory Committee
April 26	**Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in castration-resistant prostate cancer	PDUFA date
April 26	Topic **TBA**	FDA's Circulatory System Devices Advisory Committee
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

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	Other 2012	
2Q12	**Arena Pharmaceutical and Eisai's Lorqess** (lorcaserin) for weight loss	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
May TBA	**Gilead Sciences' Truvada** (emtricitabine + tenofovir) for HIV prevention	FDA's Antiviral Drugs Advisory Committee
May 1	**Protalix Biotherapeutics' taliglucerase alfa**, an investigational Gaucher disease drug	PDUFA date
May 4	**Alexza Pharmaceuticals' Adasuve** (loxapine inhalation powder) for the acute treatment of agitation associated with schizophrenia/bipolar I disorder	PDUFA date
May 13	**Talon Therapeutics' Marqibo** (vincristine sulfate liposomes injection) for Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL)	PDUFA date
May 23	**Bristol-Myers Squibb's Eliquis** (apixaban), an anticoagulant for prevention of stroke in AFib	FDA's Cardiovascular and Renal Drugs Advisory Committee
May 30-31	Discussion of **analgesic treatment of chronic pain** – mechanisms, epidemiology, new data on opioid efficacy, etc.	FDA Public Workshop
June	**Forest Laboratories and Ironwood Pharmaceuticals' linaclotide** for IBS-C	PDUFA date
June 5	**Salix Pharmaceuticals' crofelemer** for HIV-related diarrhea	PDUFA date
June 8	**Roche/Genentech's pertuzumab** in HER2+ advanced breast cancer	PDUFA date
June 15	**Gilead Sciences' Truvada** (emtricitabine + tenofovir) for HIV prevention	PDUFA date
June 25	**QRxPharma's MoxDuo** (morphine + oxycodone)	PDUFA date
June 26	**Edwards Lifesciences' Sapien** transcatheter aortic valve	CMS final NCD expected
June 29	**Astellas Pharma's mirabegron** for treatment of overactive bladder	PDUFA date
July 26	**Amarin's AMR-101** (omega-3 fish oil EPA) to treat hypertriglyceridemia	PDUFA date
July 26	**Horizon Pharma's Lodotra** (low-dose prednisone) for rheumatoid arthritis	PDUFA date
July 27	**Onyx Pharmaceuticals' carfilzomib** for multiple myeloma	PDUFA date
July 30	**Regeneron's Arcalyst** (rilonacept) for gout	PDUFA date
August 21	**Pfizer's tofacitinib**, an oral JAK2 inhibitor for rheumatoid arthritis	PDUFA date
August 27	**Gilead Sciences' Quad** (emtricitabine + tenofovir + elvitegravir + cobicistat) for HIV	PDUFA date
October 21	**Impax Laboratories' IPX-066** for Parkinson's disease	PDUFA date