TRENDS-in-MEDICINE

January 22, 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…

SHORT TAKES

- **Alzheimer's disease –** Patients who were cognitively normal when they died can still be diagnosed with Alzheimer's on the basis of autopsy findings alone, according to new guidelines endorsed by the National Institute on Aging (NIA) and the Alzheimer's Association and published in ***Acta Neuropathologica*** and in ***Alzheimer's & Dementia***.

- **AstraZeneca and Bristol-Myers Squibb's dapagliflozin –** The FDA rejected this diabetes drug, which would have been the first SGLT2 inhibitor, saying it wants more clinical data. *It looks like another clinical trial will be needed.*

- **CareFusion's Alaris System**, an intravenous drug delivery system, scored a first, gaining certification as meeting the National Institute of Standards and Technology's Federal Information Processing Standard for such devices. This certification is required for all infusion systems that wirelessly transmit sensitive data via the Department of Veterans Affairs hospital networks.

- **Columbia Laboratories and Watson Pharmaceuticals' Prochieve (progesterone gel 8%) –** The FDA's Reproductive Health Drugs Advisory Committee rejected this vaginal gel, voting that it was safe but not more effective than placebo in preventing preterm birth in women with a short cervix (≤3 cm at 24 weeks' gestation).

- **Glioblastoma –** Researchers from the University of Texas Health Science Center at San Antonio reported in ***Molecular Cancer Research*** that they have discovered a novel mechanism that may explain how glioblastoma develops. They found that two RNA-binding proteins, Musashi1 and HuR, are key regulators in glioblastoma.

- **Innate Pharma** said a discovery published in the journal ***Science*** – that mice not expressing natural killer T cells are resistant to some viral infections – may lead to new experimental drugs to fight infections. Innate Pharma plans to test NKp46 as a potential target for experimental drug candidates.

- **Napo Pharmaceuticals and Glenmark Pharmaceuticals' Provir (crofelemer) –** In December, Napo terminated a collaboration with Glenmark on this investigational drug to treat chronic diarrhea in HIV patients. However, this week a U.S. arbitration panel issued an interim order that bars Napo from ending its licensing deal with Glenmark or from considering the partnership terminated. Glenmark said the next arbitration hearing is scheduled in late March 2012.

- **Novartis' 4CMenB –** This investigational vaccine against *Neisseria meningitidis* serogroup B showed nearly universal protection in adolescents in a pivotal study in Chile that was published in ***The Lancet***. After 2-3 doses, >99% of people vaccinated developed protective titers against the four targeted test strain factors vs. 92%-97% protection rate

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with one dose ($p<0.0145$) and 29%-50% with placebo. After six months, >90% of people who got 2-3 doses still had protective titers vs. 73%-76% of those with just one dose.

- **PFIZER and MEDIVATION's Dimebon (latrepirdine)** failed in a second Phase III trial, CONCERT, in mild-to-moderate Alzheimer's disease, and the companies said they are stopping development in all indications, which includes termination of an open-label extension study in Alzheimer's.

- **ST. JUDE MEDICAL's PressureWire Aeris and PressureWire Certus** – The company said the Data Safety Monitoring Board (DSMB) recommended stopping the FAME-II trial because an interim analysis showed a highly significant reduction in re-hospitalizations and urgent revascularizations in patients with stable coronary artery disease (CAD) with optimal medical treatment (OMT) who underwent fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) vs. no PCI.

- **SANOFI's Multaq (dronedarone)** – The company plans a large, randomized, double-blind, parallel arm, placebo-controlled Phase IV trial, HARMONY, in pacemaker patients to test the safety and efficacy of combining Multaq with **Gilead Sciences' Ranexa** (ranolazine) in atrial fibrillation patients.

- **Selective serotonin reuptake inhibitors (SSRIs)** – A 248-patient study published in the ***British Journal of Clinical Pharmacology*** found that these antidepressants are associated with an increased risk of falls in nursing home residents with dementia. The researchers reported that the risk of an injury-causing fall was three times higher for residents taking an SSRI than for those who didn't take an SSRI (0.28% vs. 0.09% for an 80-year-old woman).

- **VIROPHARMA's Cinryze (C1 esterase inhibitor)**, a treatment for hereditary angioedema, obtained priority-review status from Health Canada, which is expected to make a decision in 2H12.

NEWS IN BRIEF

BAYER's Yaz and Yasmin (drospirenone) – FDA defends AdCom makeup

Last week the ***Wall Street Journal*** raised questions about the impartiality of three members of an FDA advisory committee meeting in December 2011 – the Reproductive Health Drugs Advisory Committee meeting jointly with the Drug Safety and Risk Management Advisory Committee – which voted 15-11 that the benefits of these oral contraceptives outweighed the risk of venous thromboembolism (VTE). The newspaper said these three members had ties to the company. This week, on the FDA's new blog, FDA Acting Associate Commissioner for Special Medical Programs Jill Hartzler Warner, JD, defended the AdCom process in general and the drospirenone panel specifically, writing, "Based on our review of the members' reported financial interests, we did not identify any financial interests that would have precluded their participation."

BIOGEN IDEC and ELAN's Tysabri (natalizumab) – label changed and PML risk test approved

The FDA notified doctors that a positive anti-JC virus test is now recognized as a risk factor for progressive multifocal leukoencephalopathy (PML), a rare but serious side effect of this drug for multiple sclerosis (MS) and Crohn's disease. The FDA said a patient's anti-JCV antibody status may be determined using an anti-JCV antibody detection test that has been analytically and clinically validated (the first of which is **Quest/Focus Diagnostics' Stratify JCV Antibody ELISA Test 2**).

The FDA recommended that patients weigh the risks and benefits of continuing treatment with Tysabri if they are found to be anti-JCV antibody-positive and have ≥1 known risk factor for PML. The Agency estimated that patients with all three known risk factors have an estimated PML risk of 11:1,000. The FDA-recognized risk factors that increase the chance of Tysabri-treated patients developing PML are:

- JCV-antibody positivity.
- Treatment with Tysabri >2 years.
- Treatment with immunosuppressants before Tysabri.

The FDA updated the Tysabri label to include information that testing positive for anti-JCV antibodies is a recently identified risk factor for developing PML in patients treated with Tysabri for MS or Crohn's. The FDA also warned that the Stratify JCV Antibody ELISA test should ***not*** be used on its own as a basis for determining the risk for developing PML in patients on immunomodulatory therapy or for making clinical decisions and that the test cannot be used to diagnose PML. And the FDA emphasized that the test is for professional use and by prescription only and is to be performed only at Focus Diagnostics' Reference Laboratory. The Agency also said the test is ***not*** intended for blood donor screening.

Bone densitometry – frequent testing may not be necessary

A study published in the ***New England Journal of Medicine*** suggested that postmenopausal women who had good bone

mineral density (BMD) at an initial osteoporosis screening could probably wait ~15 years before the next test. Based on the amount of time it took for 10% of women ≥age 67 to progress to osteoporosis, the testing intervals were:

- 16.8 years for women with normal bone mineral density.
- 17.3 years for women with mild osteopenia.
- 4.7 years for women with moderate osteopenia.
- 1.1 years for women with advanced osteopenia on initial testing.

BRISTOL-MYERS SQUIBB's daclatasvir (an NS5A polymerase inhibitor) and asunaprevir (an NS3 protease inhibitor) – two oral agents with no interferon cure HCV

In a Phase II trial published in the ***New England Journal of Medicine***, 36% of hepatitis C patients who hadn't responded to previous therapy and were given a combination of these two direct-acting antiviral agents – without pegylated interferon or ribavirin – achieved sustained virologic response (SVR) at 12 weeks (the primary endpoint) and at 24 weeks after the end of treatment.

The researchers said the study was a "proof-of-concept." In another arm of the study, in which patients received both drugs plus pegylated interferon and ribavirin (a four-drug combo), 100% of the patients achieved SVR at 12 weeks after stopping treatment, and 90% still had undetectable virus at 24 weeks post-treatment. Six patients – all with genotype 1a – had viral breakthrough on therapy, and all of these developed resistance mutations to both agents. The most common adverse event was diarrhea, and six patients had transient elevations of ALT >3xULN.

Extracorporeal membrane oxygenation (ECMO) – a bridge to lung transplantation

Extracorporeal membrane oxygenation support in awake, non-intubated patients may be an effective strategy for bridging patients to lung transplantation, according to a 60-patient, retrospective, single-center study from Germany that was published in the American Thoracic Society's ***American Journal of Respiratory and Critical Care Medicine***.

Of 26 patients in the ECMO group, 23% died before a donor organ became available vs. 29% of patients in the mechanical ventilation group. Among the patients who reached transplantation, the survival rate at six months post-transplantation was significantly higher in the awake ECMO group vs. the mechanical ventilation patients (80% vs. 50%, p=0.02), though awake ECMO patients who required secondary intubation only had a 43% survival rate.

Rheumatoid arthritis (RA) – muscle relaxants and neuromodulators don't work

A study by Australian researchers, published in ***The Cochrane Library***, found that muscle relaxants and neuromodulators do not work as well as expected to manage pain in patients with RA. The researchers reported that benzodiazepines (diazepam and triazolam) do not appear to improve pain over 24 hours or 1 week, and zopiclone, a non-benzodiazepine, also did not significantly reduce pain over 2 weeks. And even short-term use of muscle relaxants was associated with adverse events, including dizziness and drowsiness.

There was weak evidence in the study that neuromodulators – oral nefopam, topical capsaicin, and oromucosal cannabis – were superior to placebo in reducing pain, but each of these drugs also is associated with adverse events. However, the researchers suggested that using capsaicin as add-on therapy for patients with persistent local pain and inadequate response or intolerance to other treatments might be considered because patients reported a 34% absolute improvement in pain rating scores with it.

ROCHE's Tamiflu (oseltamivir) – efficacy challenged

An independent review by the non-profit Cochrane Collaboration, published in the ***British Medical Journal***, raised questions about the efficacy and safety of this anti-flu drug. The analysis found that Tamiflu reduced the duration of flu symptoms by ~21 hours but could not confirm that Tamiflu reduces hospitalizations or pneumonia. And the researchers complained that the company hasn't allowed access to much of the data on Tamiflu, not only to them but to the European Medicines Agency (EMA). One of the investigators, Peter Doshi, PhD, from Johns Hopkins University, said, "What we're seeing are largely Chapter 1 and Chapter 2 of reports that usually have 4-5 chapters."

ROCHE's Zelboraf (vemurafenib) – melanoma benefit comes at a price

A study published in the ***New England Journal of Medicine*** found that this BRAF inhibitor treatment for melanoma actually speeds the growth of another type of skin cancer, cutaneous squamous cell carcinoma, in about a third of patients. The researchers reported that Zelboraf blocks the mutation that makes melanoma grow, but if patients have skin cells with a RAS mutation (that's probably induced by sun exposure), then Zelboraf has the exact opposite effect, causing

squamous cell cancers to grow. However, the researchers suggested that combining Zelboraf with a MEK inhibitor, which blocks the RAS mutation, may prevent both the squamous cancers and the melanoma.

In an accompanying editorial, Ashani Weeraratna, PhD, of the Wistar Institute in Philadelphia, advised doctors to know a patient's RAS status before treating with Zelboraf (or any other BRAF inhibitor).

Statins – a cancer therapy?

A study published in ***Cell*** found that statins may help prevent or treat certain cancers – e.g., breast cancer – in patients with mutant forms of the p53 tumor suppressor gene, which is responsible for stopping uncontrolled growth of cancer cells. Laboratory studies showed that tumor cells stopped their erratic growth and some even died when statins were administered.

THE MEDICINES COMPANY's cangrelor – positive "bridging" study published

The 210-patient, multicenter BRIDGE study, published in the ***Journal of the American Medical Association***, found that this investigational intravenous antiplatelet drug maintained low platelet reactivity (by **Accumetrics' VerifyNow** assay) in patients who must discontinue therapy with a thienopyridine – **Sanofi's Plavix** (clopidogrel) or **Lilly's Effient** (prasugrel) – before undergoing CABG. In the study, 98.8% of cangrelor patients had low platelet reactivity in the days prior to surgery vs. 19% of Plavix/Effient patients. The benefits were achieved without an increase in major bleeding.

Tyrosine kinase inhibitors – early help, late harm?

Harvard Medical School researchers warned, based on a mouse study published in ***Cancer Cell***, that tyrosine kinase inhibitors (TKIs) may shrink tumors, but they promote metastases in other parts of the body. They suggested that **Novartis' Gleevec** (imatinib) and **Pfizer's Sutent** (sunitinib), which are designed to shrink tumors by cutting off their blood supply, may be doing the opposite – helping them spread. The researchers studied pericytes, which provide structural support to the blood vessels and help stop tumor growth, and found they can be wiped out by cancer drugs.

The problem, the researcher said, is that Gleevec and Sutent may improve survival in the short term but eventually could make the cancers more deadly by promoting metastases. They removed pericytes from breast cancer tumors in genetically engineered mice. Initially, they saw a 30% decrease in tumor growth in the mice – but a three-fold increase in secondary lung tumors.

The study also found a five-fold increase in cancer tumors that spread in oxygen-starved areas, which had few pericytes. The researchers discovered that smaller tumors shed more cancer cells into the bloodstream than larger tumors with a good supply of pericytes.

REGULATORY NEWS

FDA issues guidance on IDEs and INDs for knee repair products

The FDA issued guidance on proper submissions for investigational device exemption (IDE) and investigational new drug (IND) applications for products intended to repair or replace knee cartilage. The guidance – which covers devices, biologics, and hybrid products – outlines items that must be included in submission documents, including written description of individual components, materials, anticipated changes, and evidence that device materials are safe for limited contact with a breached surface. The FDA said the new guidance does not apply to prostheses such as total or unicondylar knee replacements.

FDA news

- **Chemical reactions.** Industry experts are concerned that the FDA's definition of a "chemical reaction" used to rule out a product as a device is subjective and too broad. The FDA's definition is: If a product facilitates cellular or molecular response or if it changes an entity to influence its interaction with a human's or an animal's body, it is ***not*** a device.
- **Devices.** The Agency missed the January 15, 2012, deadline to submit its proposal for user fees to accelerate medical device reviews.
- **Primary care drugs.** The FDA's lack of clear guidance on how it views risk:benefit for primary care drugs is hampering drug development, the chairman of Pharmaceutical Research and Manufacturers of America (PhRMA) said.

FDA approvals/clearances

- **AGFA HEALTHCARE's DX-M** computed radiography digitizer was cleared.
- **BTG INTERNATIONAL's Voraxaze (glucarpidase)** was approved to reduce dangerous levels of methotrexate in cancer patients with failing kidneys.

- **IVERA MEDICAL's Curos**, a disinfecting port protector to lower the risk of catheter-based bloodstream infections, received 510(k) clearance.
- **KONICA MINOLTA MEDICAL IMAGING's Xpress CR**, a digital mammography upgrade, was cleared for use.

FDA recalls/warnings

- **COVIDIEN's Duet TRS** – The company initiated a voluntary recall of these thoracic surgery devices.
- **JOHNSON & JOHNSON/DEPUY** – The FDA issued a warning letter saying that the company marketed 14 custom hip and knee replacements without notifying the Agency or seeking necessary approval. The company said that it thought it had complied with FDA regulations but has decided "at this time not to provide custom devices."

European regulatory actions

- **CEPTARIS THERAPEUTICS' mechlorethamine gel (chlormethine gel in Europe)**, an investigational drug for cutaneous T-cell lymphoma (CTCL), was granted orphan drug status by the European Medicines Agency (EMA). It already has U.S. orphan drug status.
- **SANOFI/GENZYME's Fabrazyme (agalsidase beta)** – The EMA said Genzyme may produce this Fabry disease treatment at the company's Framingham MA plant. The company is still waiting for FDA approval to produce it at that plant.

Asian regulatory actions

- **NOVARTIS' Galvus (vildagliptin)** – The Chinese State Food and Drug Administration approved this diabetes drug as add-on therapy for Type 2 diabetes.
- **NOVARTIS' Lucentis (ranibizumab)** – The Chinese State Food and Drug Administration approved Lucentis to treat wet age-related macular degeneration (AMD).
- **XENOPORT and ASTELLAS PHARMA's Regnite (gabapentin enacarbil)** was approved in Japan as a treatment for moderate-to-severe restless legs syndrome.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	January 2012	
January 28	**Eli Lilly, Amylin Pharmaceuticals, and Alkermes' Bydureon** (weekly exenatide XR), an injectable drug for Type 2 diabetes	FDA decision date
January 30	Discussion of pediatric-focused drug safety reviews for **Novartis/Celgene's Focalin XR** (dexmethylphenidate), **Shire's Daytrana** (methylphenidate), **AstraZeneca's Seroquel** (quetiapine), **Johnson & Johnson's Pancreaze** (pancrelipase amylase), **Aptalis' Zenpep** (pancrelipase lipase), **Abbott's Creon** (pancrelipase protease), plus discussion of **Teva's Plan B One-Step**.	FDA's Pediatric Advisory Committee
January 31	Pediatric-focused safety reviews on vaccines, including **Pfizer's Prevnar 13** for pneumonia and **GlaxoSmithKline's Cervarix** for HPV	FDA's Pediatric Advisory Committee
	February 2012	
February 1	Reauthorization of **PDUFA-V**	Health subcommittee of House Energy and Commerce Committee hearing
February 4	**Alexza Pharmaceuticals' Adasuve** (loxapine inhalation powder) for the acute treatment of agitation associated with schizophrenia/bipolar I disorder	PDUFA date
February 7	FDA's proposed **user fees for biosimilars**	Health subcommittee of House Energy and Commerce Committee hearing
February 8	**Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in castration-resistant prostate cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
February 9	**Eisai's Dacogen** (decitabine) for treatment of acute myelogenous leukemia (AML) and **Cell Therapeutics' Pixuvri** (pixantrone dimaleate) for relapsed/refractory non-Hodgkin's lymphoma	FDA's Oncologic Drugs Advisory Committee
February 9	**NeurogesX's Qutenza** (transdermal capsaicin) for HIV-related neuropathic pain	FDA's Anesthetic and Analgesic Drug Products Advisory Committee
February 10	Possible reclassification of **cranial electrotherapy stimulator (CES) devices** to Class III (requiring a PMA)	FDA's Neurological Devices Advisory Committee
February 15	Reauthorization of **FDA user fee program for medical devices**	Health subcommittee of House Energy and Commerce Committee hearing
February 17	**Corcept Therapeutics' Corlux** (mifepristone) for Cushing's syndrome	PDUFA date
February 22	**Vivus' Qnexa** (phentermine + topiramate), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
February 23	**Chelsea Therapeutics' Northera** (droxidopa) for symptomatic neurogenic orthostatic hypotension with primary autonomic failure	FDA's Cardiovascular and Renal Drugs Advisory Committee
February 27	Review of evidence needed for approval of **anti-inflammatory ophthalmic drugs post-ocular surgery** and appropriateness of marketing a single bottle for use in both eyes post-surgery	FDA's Dermatologic and Ophthalmic Drugs Advisory Committee
	March 2012	
March 6	**Discovery Labs' Surfaxin** (lucinactant) for infant respiratory disease	PDUFA date
March 7	**NeurogesX's Qutenza** (transdermal capsaicin) for neuropathic pain	PDUFA date
March 8	**Roche/Genentech and Curis' vismodegib** for advanced basal cell carcinoma in adults for whom surgery is not an option	PDUFA date
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	**Pfizer's Inlyta** (axitinib) for advanced renal cell carcinoma	PDUFA date
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
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

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
April 2012		
April 17	**Vivus' Qnexa** (phentermine + topiramate) for weight loss	PDUFA date for resubmission
April 18	**Vertex Pharmaceuticals' Kalydeco** (ivacaftor) for cystic fibrosis	PDUFA date
April 24	**Cell Therapeutics' pixantrone** for aggressive non-Hodgkin's lymphoma	PDUFA date
April 25	**Takeda's alogliptin**, a DPP-4 for Type 2 diabetes	PDUFA date
April 26	**Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in castration-resistant 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
Other 2012		
May 1	**Protalix Biotherapeutics' taliglucerase alfa**, an investigational Gaucher disease drug	PDUFA date
June	**Forest Laboratories and Ironwood Pharmaceuticals' linaclotide** for IBS-C	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