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…

Trends-in-Medicine
Stephen Snyder, *Publisher*
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409
Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

SHORT TAKES

- **ACCELRYS** acquired **VelQuest**, which produces software for FDA-regulated industries such as pharmaceuticals and biotech.
- **ACHILLION PHARMACEUTICALS' ACH-1625,** which is in Phase II development to treat HCV, was granted fast track status by the FDA.
- **Alliance for Continuing Medical Education (CME)** changed its name to the **Alliance for Continuing Education in the Health Professions**.
- **AVEO PHARMACEUTICALS and ASTELLAS PHARMA's tivozanib –** The company said the drug met the primary endpoint in a Phase III trial in advanced kidney cancer. Progression-free survival was 11.9 months with tivozanib vs. 9.1 months with **Bayer/ Onyx's Nexavar** (sorafenib). The company plans to submit the drug to both U.S. and European regulators later this year.
- **BIOMIMETIC THERAPEUTICS' Augment –** The FDA said the company must submit additional clinical data before the Agency will approve the premarket approval (PMA) application for this bone graft device for use in foot and ankle surgeries. The FDA also reportedly wants additional information on planned postmarketing studies of potential carcinogenicity and pharmacokinetics. However, the company said it may not need to do another clinical trial.
- **BRISTOL-MYERS SQUIBB** is buying **Inhibitex**, which has INX-189, an oral nucleotide polymerase (NS5B) inhibitor in Phase II development to treat hepatitis C virus (HCV).
- ***Clostridium difficile (C. diff)* –** A review published in the ***Annals of Internal Medicine*** found that no antibiotic is superior as the first-line treatment for *C. diff*, with initial cure rates comparable to vancomycin and metronidazole and only marginally better for **Optimer Pharmaceuticals and Astellas' Dificid** (fidaxomicin). The researchers concluded, "More liberal use of vancomycin is reasonable."
- **CSL BEHRING's Berinert (C1 esterase inhibitor) –** The FDA is letting patients with acute hereditary angioedema (HAE) administer this drug to themselves intravenously after they get training from a healthcare professional.
- **DURECT's Posidur (SABER-bupivacaine) –** The pivotal U.S. Phase III trial (BESST) of this long-acting anesthetic for pain relief for abdominal surgery failed.
- **HALO THERAPEUTICS' HT-100 (halofuginone)** was granted orphan drug status for Duchenne muscular dystrophy, and it will start a Phase II trial later this year.

- **JOHNSON & JOHNSON's Doribax (doripenem)** – A clinical trial of this antibiotic in pneumonia was halted because mortality was higher – and the cure rate lower – in the drug arm than in the placebo arm. However, the FDA said the drug is still considered safe and effective for treating its approved indication – urinary and abdominal infections. *The question now is whether European approval for hospital-acquired pneumonia will be withdrawn.*

- **LIPOSCIENCE's Vantera** – The company submitted a 510(k) application for this nuclear magnetic resonance analyzer for diagnosing heart disease. The device would allow hospitals and research centers to conduct in-house analyses of LipoScience's lipoprotein density blood tests.

- **Nanotechnology** – A coalition of consumer advocacy groups led by the International Center for Technology Assessment filed a lawsuit against the FDA demanding a response – which has not been forthcoming – to a 2006 petition that asked the Agency to require labeling of nano-tech ingredients in consumer products.

- **ORIDION SYSTEMS** was barred by the FDA from shipping its medical devices to the U.S. after the Israeli device firm reportedly failed to resolve quality issues at its manufacturing plant in Jerusalem.

NEWS IN BRIEF

Age-related macular degeneration (AMD) – linked to daily aspirin use

A large European study published in ***Ophthalmology***, the journal of the American Academy of Ophthalmology, found that people age ≥65 who take aspirin daily had double the risk of developing this vision-threatening eye disorder. The 839-patient study found that patients taking daily aspirin had higher rates of cardiovascular disease, were less likely to be smokers, and were older than participants who took aspirin less often. However, even when cardiovascular status was factored in, the results found a higher risk for wet AMD in daily aspirin users.

The researchers did not recommend that doctors stop recommending daily aspirin for elderly people or for cardiovascular disease patients – at least not until this study is confirmed. Paulus de Jong, MD, PhD, of the Netherlands, who led the research team, said, "It's possible that increased AMD risk may outweigh aspirin's potential protective benefits for some patients, but we need to know more about the impacts of dose, length of use, and other factors before we can say for certain or make specific recommendations."

ARENA PHARMACEUTICALS and EISAI's Lorqess (lorcaserin) – resubmitted to FDA

The company submitted additional data to the FDA on this diet drug in an effort to address FDA concerns about breast tumors in female rats. The data included both Phase III trial data in patients with Type 2 diabetes and animal data that reportedly showed that rats getting high-dose Lorqess did not develop malignant tumors. Arena claims Lorqess increases prolactin, a hormone that triggers malignancy formation in rats but not humans.

Atrial fibrillation – catheter ablation efficacy questioned

A study of 4,156 patients in a California database who had catheter ablation for atrial fibrillation (AFib) – published in the ***Journal of the American College of Cardiology*** – found that 5.1% developed complications while hospitalized, including bleeding, tamponade, or perforation. In addition, Stanford University researchers and colleagues reported that 9.4% of patients were rehospitalized within 30 days, often for AFib or flutter. Patients who developed complications had a mean length of stay in the hospital of 3.42 days vs. 1.46 days for those without complications ($p<0.001$).

Rehospitalization was more common in women, in patients with a higher number of prior hospitalizations for AFib in the prior year, in patients age 75-84, and in patients getting the procedure at less experienced hospitals. By 1 year, 61.5% of patients had not been rehospitalized for any cause, and 78.3% had not been readmitted for recurrent arrhythmia or repeat ablation. At 2 years, 70.4% had not been rehospitalized for arrhythmia or ablation. However, the researchers looked at this the other way, noting that the readmission rate was 22% at 1 year and 30% at 2 years, which they said suggests that "ablation has limited success in preventing arrhythmia recurrence over longer-term follow-up."

GILEAD's Truvada (emtricitabine + tenofovir) – prevention trial to begin

The first trial is scheduled to begin in France later this month testing this HIV drug as a preventive agent vs. placebo in men who have anal sex with men without the routine use of a condom but who do not yet have HIV. The investigators plan to enroll 1,900 seronegative volunteers and will follow them for 12-48 months. In addition to following the men's HIV status, the study, sponsored by the French National Agency for Research on AIDS and Viral Hepatitis (ANRS), will analyze how compliant they are with taking their medications.

MEDTRONIC's Infuse (bone morphogenetic protein-2, BMP-2) – safety study under way

Two separate studies are planned to determine the safety of this bone growth product used in spine surgery. Researchers at Yale University, with funding from Medtronic, are supervising both studies – one in the U.K. and one at Oregon Health & Science University (OHSU). Each team will issue a separate report, in Portland, with both reports expected in summer 2012.

Multiple sclerosis – Epstein-Barr virus link

A U.K. study published in ***Neurology*** suggests that the Epstein-Barr virus may actually play a role in multiple sclerosis (MS) after all – by activating innate immune responses. The researchers examined brain tissue postmortem and found the Epstein-Barr virus infected cells and over-expression of interferon-alpha in active white matter MS lesions but not inactive lesions or normal controls.

REGENERON PHARMACEUTICALS' Arcalyst (rilonacept) – positive data in gout

An 83-patient, 12-week, Phase II study published in ***Arthritis and Rheumatism***, a journal of the American College of Rheumatology, found that adding this IL-1 inhibitor – which is FDA-approved to treat cryopyrin-associated periodic syndromes (CAPS) – to allopurinol significantly reduced acute gout flares that occur when initiating uric acid-lowering therapy. At 12 weeks, 15% of Arcalyst patients had a gout flare vs. 45% of placebo patients.

Silicone breast implants – the growing PIP problem

The U.K. health secretary ordered British clinics to quickly provide reliable statistics on how many of **Poly Implant Prothese's PIP silicone gel implants** (also sold as Rofil M-implants) have ruptured or oozed. French regulators recommended removal of PIP implants in the 30,000 French women who got them, but British regulators have not – yet – recommended routine removal. PIP and Rofil M-implants were not implanted in the U.K., but some British women got them at other European sites.

Statins linked to lung disease – study looks at smokers

Statins may increase the risk of interstitial lung disease in smokers, according to a study published in the ***American Journal of Respiratory and Critical Care Medicine***. Researchers at Brigham and Women's Hospital studied current and former smokers in the COPDGene trial and found that statin users had a 60% increase in the odds of having interstitial lung abnormalities vs. non-statin patients. The problem was greater for statins with high hydrophilicity, such as pravastatin.

In an accompanying mouse study, the researchers found that pre-treatment with pravastatin exacerbated bleomycin-induced lung fibrosis. And in an *in vitro* study, statin pre-treatment enhanced NLRP3 inflammasome activation through mitochondrial reactive oxygen species generation in macrophages.

The researchers cautioned that the cardiovascular benefits of statins probably outweigh the risk of developing lung abnormalities, but they said clinical workers should be aware of the possibility of patients on statins developing lung disease.

ST. JUDE MEDICAL's Amplatzer – study stopped; results a mystery

The company announced that the RESPECT trial of Amplatzer – to close a patent foramen ovale to prevent recurrent strokes in patients who had a cryptogenic first stroke – met a stopping rule that was triggered when the study met the protocol-required number of primary events. However, the trial has four stopping rules, including one for futility, and St. Jude did not disclose any of the results, not even top-line results. The findings are expected to be reported at a medical conference this year.

Transvaginal mesh – FDA orders safety studies

In September 2011, the FDA's Obstetrics and Gynecology Devices Advisory Committee recommended that manufacturers conduct a study to evaluate the risks of this surgical product used in treating urinary incontinence, and the FDA this week agreed, telling the 33 mesh manufacturers to plan and conduct safety studies.

The FDA also is considering reclassifying mesh as a high-risk device. If that happens, manufacturers would have to prove a new product's safety and effectiveness before marketing it, but no decision is expected soon.

Vaccine news

- **HIV vaccine a step closer to reality.** In a study published in the journal ***Nature***, researchers found that an experimental vaccine protected some monkeys against infection with a simian immunodeficiency virus (SIV) – the monkey equivalent of HIV. The study, which was partially funded by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health (NIH), found

vaccinated monkeys were up to 83% less likely than control monkeys to get SIV.

- **OKAIROS' hepatitis C vaccine shows promise.** A Phase I study published in ***Science Translational Medicine*** of this experimental HCV vaccine had promising results, with healthy volunteers generating an immune response against HCV that lasted for a year.
- **Herpes simplex virus vaccine falls short.** An 8,300-patient study published in the ***New England Journal of Medicine*** found that this vaccine failed – showing only 58% effectiveness at preventing genital disease caused by HSV-1 and no effectiveness against HSV-2, for an overall efficacy of 20%.

REGULATORY NEWS

FDA and DEA accused of delaying hydrocodone rescheduling decision

Sen. Kirsten Gillibrand (D-NY) sent a letter to the Drug Enforcement Administration and the FDA, accusing them of "dragging their feet" on a decision over whether to tighten controls on the painkiller hydrocodone. Currently, pure hydrocodone is a Schedule II drug, but combination products are in the less strict Schedule III category.

FDA approvals/clearances

- **CYBERONICS' AspireHC generator** – The revised version of this device that is used in patients implanted with the company's **VNS Therapy System**, to treat refractory epilepsy and treatment-resistant depression, was cleared.
- **MEDTRONIC's mySentry Remote Glucose Monitor**, which allows parents to remotely follow a diabetic child's glucose level, was approved.
- **NINEPOINT MEDICAL's Nvision VLE Imaging System** for real-time evaluation of tissues and organs was cleared.
- **VIOGUARD's germ-killing computer keyboard** was cleared for use in clinics and hospitals. After use, the keyboard withdraws into a compartment where it is sanitized by ultraviolet light.

FDA recalls/warnings

IKARIA's INOmax DS Drug Delivery System – A Class I recall was initiated because of erratic nitric oxide (NO) readings that were occurring due to fretting corrosion at the electrical contact interface of certain metals, which can cause hypoxia, hypotension, bradycardia, cardiac arrest, organ damage, acute respiratory distress syndrome (ARDS), neurological deficits, or death. The company has implemented a process change to resolve the issue.

European regulatory actions

ROCHE's COBAS AmpliPrep/COBAS TaqMan HCV Qualitative Test, v2.0 and **COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, v2.0** were both approved for HCV testing.

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 11	**Torax Medical's LINX Reflux Management System** to treat the symptoms associated with gastroesophageal reflux disease (GERD)	FDA's Gastroenterology and Urology Devices Advisory Committee
January 20	Efficacy of **Columbia Laboratories' progesterone gel 8%** to reduce the risk of preterm birth in women with short uterine cervical length	FDA's Reproductive Health Drugs Advisory Committee
January 28	**Bristol-Myers Squibb and AstraZeneca's dapagliflozin**, a first-in-class SGLT2 inhibitor for Type 2 diabetes	PDUFA date
January 28	**Eli Lilly, Amylin Pharmaceuticals, and Alkermes' Bydureon** (weekly exenatide XR), an injectable drug for Type 2 diabetes	FDA decision date
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), and others. **Teva's Plan B One-Step** also will be discussed.	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	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation
February 4	**Alexza Pharmaceuticals' Adasuve** (loxapine inhalation powder) for the acute treatment of agitation associated with schizophrenia/bipolar I disorder	PDUFA date
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 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 tba	**Anti-nerve growth factor (NGF)** drug class safety review	FDA's Arthritis Advisory Committee
March 6	**Discovery Labs' Surfaxin** (lucinactant) for infant respiratory disease	PDUFA date
March 7	**NeurogesX's Qutenza** (transdermal capsaicin) for HIV-related 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 13	**Pfizer's Inlyta** (axitinib) for advanced renal cell carcinoma	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

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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
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