Trends-in-Medicine

Quick Takes

by Maude Campbell and Lynne Peterson

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

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Check out the new *Trends-in-Medicine* blog on our website (www.trends-in-medicine.com). The latest entry is about healthy eating.

…Highlights from this week's news affecting drugs and devices in development…

SHORT TAKES

- **ALCON** is acquiring privately-held **LenSx** for $361.5 million in cash plus up to $382.5 million based upon the achievement and over-achievement of future femtosecond laser and procedure fee revenue milestones. *What does this say about the viability of Alcon/WaveLight's own femtosecond laser?*
- **ASPEN PHARMACARE HOLDINGS – *Bloomberg*** reported that Aspen lowered the price it is offering to acquire **Sigma Pharmaceuticals** by 8.3% to $550 million, after perusing the company's books.
- **BECKMAN COULTER's AccuTnI –** The company received a warning letter from the FDA charging that changes were made to this troponin I test, and it was marketed without FDA approval of the changes. The company said it plans to conduct a clinical trial and file applications with the agency in 1H11.
- **CARDIONET's MCOT –** UnitedHealth Group has denied coverage for MCOT, a mobile-cardiovascular telemetry technology used for managing irregular heart rhythm.
- **CORNERSTONE THERAPEUTICS' Zyflo CR (zileuton) –** The FDA sent the company a warning letter saying promotion materials withheld information about the risks of this asthma drug, used "outdated labeling," and suggested Zyflo CR is more effective than competing drugs like Merck's Singulair (montelukast). In addition, the FDA said a visual aid did not include warnings about the most serious or most common side effects.
- **DYNAVAX** received a $600,000 grant from the National Institutes of Health (NIH) to help fund its research on a vaccine that protects against most cancer-causing strains of human papillomavirus (HPV).
- **FOREST LABORATORIES/CEREXA's ceftaroline fosamil for injection** will be reviewed by the FDA's Anti-Infective Drugs Advisory Committee on September 7, 2010. In the morning the panel will consider an indication for the treatment of

adults with community-acquired bacterial pneumonia (CABP), and in the afternoon the panel will consider an indication for complicated skin and skin structure infections (cSSSI).

- **LILLY** has signed a definitive merger agreement to acquire **Alnara Pharmaceuticals**, which is awaiting FDA review of its liprotamase, a non-porcine pancreatic enzyme replacement therapy for exocrine pancreatic insufficiency, a condition often associated with cystic fibrosis. Financial details were not disclosed.

- **MEDICIS' LipoSonix –** The FDA said it cannot approve this ultrasound lipolysis (liposuction) device without additional data, noting the data submitted were "not sufficient to approve the device." Medicis claimed to have the additional data needed and insisted the issue "has nothing to do with safety."

- **MEDTRONIC** received a warning letter from the FDA charging that its surgical navigation tools unit – which makes defibrillators, pacemakers, and spinal devices – failed to create and maintain processes for monitoring complaints and validating device designs, etc. The FDA indicated Medtronic is working to resolve the problems.

- **MERCK KGAA**, in a joint venture with **Vaximm Holding**, will start clinical trials with an experimental cancer vaccine in 2011, beginning with a trial in 40 patients with advanced pancreatic cancer.

- **RANBAXY –** As part of its R&D merger with Daiichi Sankyo, Ranbaxy transferred new drug research responsibilities to Daiichi Sankyo's Life Science Research Center in India. The center will focus on treatments for infectious and inflammatory diseases, dengue fever, and tuberculosis.

- **ROCHE's trastuzumab-DM1** has been submitted to the FDA – based on Phase II data – for the treatment of advanced HER2-positive breast cancer in women who have previously received multiple HER2-targeted medicines and chemotherapies.

- **SANOFI-AVENTIS** will pay $75 million to acquire **TargeGen** in a deal that may garner TargeGen up to $560 million if its lead product, TG-101348, in development for treatment of myelofibrosis, is eventually approved.

- **Technetium-99 shortage news –** The Chalk River nuclear reactor has been cleared by Canadian authorities to resume operation, which means it should be producing isotopes by the end of July 2010.

- **URL PHARMA's Colcrys (colchicine) –** Some rheumatologists said that URL threatened (*tried to intimidate?*) them with a lawsuit because of statements on their blog, which urged colleagues to use inexpensive generic colchicine instead of Colcrys.

- **VIVUS's Qnexa (phentermine + topiramate) –** According to a ***Bloomberg*** report, FDA officials said the heart valve problems associated with fen-phen will not be part of the discussion of Qnexa at the advisory committee meeting on July 15, 2010, because the problem with fen-phen was the fenfluramine and dexfenfluramine due to the particular receptor that they activate.

NEWS IN BRIEF

ALLERGAN's Botox (onabotulinumtoxinA) – gets U.K. migraine approval

As anticipated, the U.K. Medicines and Healthcare Products Regulatory Agency approved Botox for the treatment of chronic migraine. However, Allergan said it expects that the National Institute for Health and Clinical Excellence (NICE) will take several months to determine whether Botox will be reimbursed when used for the headache disorder.

Meanwhile, similar migraine Botox approval decisions are expected 3Q10 in France and Switzerland, and if Ireland, a reference member state for European Union (EU) markets, approves use in migraine, it will be licensed in other EU states as long as those states do not object. Allergan said it continues to expect the FDA to decide whether to approve Botox for chronic migraine sometime in July 2010, and it anticipates a potential U.S. launch in 4Q10. However, if the FDA requires additional information, Allergan said there will be a delay of up to 3 years.

AR SCIENTIFIC's Qualaquin (quinine) – not for RLS

The FDA is warning against off-label use of this malaria drug to prevent or treat leg cramps or restless leg syndrome. The Agency said the off-label uses have resulted in serious adverse events, including thrombocytopenia and hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, sometimes causing hospitalization and permanent kidney damage and resulting in at least 2 deaths. The company is now instituting a risk evaluation and management strategy (REMS) which will include a Medication Guide for patients and a Dear Healthcare Professional letter to doctors.

ASTRAZENECA's olaparib (AZD-2281) – possible utility in genetic forms of breast and ovarian cancer

The U.K.'s ***Daily Mail*** reported that a study of 111 women with advanced, refractory inherited breast or ovarian cancer found olaparib, a PARP inhibitor, dramatically shrank tumors in 40% of breast cancer patients getting the high dose and in 33% of ovarian cancer patients.

CAMBRIDGE HEART's T-wave Alternans – reimbursement looking up

Under new CMS rules, MTWA (microvolt T-wave alternans) tests performed during the same visit as a cardiac stress test can be fully reimbursed. And in other news, the first patients out of the planned 200 were enrolled in the MTWA-CAD trial to evaluate whether MTWA technology can be used to augment current testing methods that depict ischemia, such as cardiac stress testing.

CATALYST PHARMACEUTICAL PARTNERS' vigabatrin – patent granted for addiction prevention

The European Patent Office granted Brookhaven Science Associates/Brookhaven National Laboratory a European patent for the use of vigabatrin, a GABA aminotransferase inhibitor, for the prevention of addiction to opioids (e.g., oxycodone, hydrocodone) used in pain management. By dampening dopamine release and thus, the euphoria associated with opioids, an opioid/vigabatrin combination may lower or prevent addictive liability without adversely affecting pain relief. Neuroscientists at North Shore-Long Island Jewish Health System are conducting a Department of Defense-funded animal study of vigabatrin + opioids to test this hypothesis.

Centers for Medicare and Medicaid Services (CMS)

- **New chief named.** President Barack Obama used a recess appointment to make Dr. Donald Berwick the administrator of CMS. A ***Washington Post*** reporter said Dr. Berwick, a pediatrician and Harvard professor, has a reputation as a "zealot and an entrepreneur when it comes to quality improvement." Much of the controversy comes from this comment by Dr. Berwick: "The decision is not whether or not we will ration care. The decision is whether we will ration with our eyes open."
- **Proposing to change the way skin substitutes are reimbursed.** Currently, CMS uses a "global" period of service, which means that a provider can only bill for use of a skin substitute once in a 90-day (or occasionally a 10-day) period. However, CMS has proposed allowing Medicare to be billed for each visit in which a skin substitute is used, for example for diabetic foot ulcers. The Agency is accepting comments for the next 60 days, and any final decision would likely go into effect on January 1, 2011. This change could benefit both Advanced BioHealing's Dermagraft and Organogenesis's Apligraf.

Chemotherapy – possible booster found

Researchers at the Translational Genomics Research Institute in Arizona reported that when they used a drug to turn off the CHEK1 gene, ovarian cancer cells stopped growing and then could be killed with cisplatin.

Fibrin sealants – FDA warns about off-label use

Because the FDA received reports of air or gas embolism occurring during or immediately after application of hemostatic drug or biological products using air- or gas-pressured sprayers, the labels for all FDA-approved fibrin sealants – e.g., Johnson & Johnson's Evicel and Baxter's Tisseel and Artiss – have been updated to emphasize the risk of air embolism and the need to use the recommended ranges of pressure and distance. The labeling change for these devices/products also includes information on recommended pressures and distances.

The adverse events appear to be related to use of spray devices inconsistent with the approved product labeling and instructions for use. In some reports the device was used at higher-than-recommended pressure or at a distance too close to the surface of the bleeding site. Although rare, the reports describe air embolisms that are life threatening and include one fatality.

GENZYME – expanded manufacturing deal with Hospira

Hospira will now do "fill and finish" manufacturing for seven Genzyme drugs – Cerezyme (imiglucerase), Fabrazyme (agalsidase beta), Myozyme (alglucosidase alfa), Lumizyme (alglucosidase alfa), Thyrogen (thyrotropin alfa), Thymoglobulin (anti-thymocyte globulin), and Campath (alemtuzumab) as well as some investigational drugs.

GRACEWAY PHARMACEUTICAL's (imiquimod 3.75%) – FDA accepts NDA for external genital warts

The FDA has accepted a New Drug Application (NDA) for the new imiquimod potency as a potential ***topical*** treatment for external genital warts. The company submitted Phase III trial data showing that the stronger imiquimod cream was more efficacious for eradicating external genital warts than imiquimod 2.5% cream. Both treatments were applied once daily for 8 weeks. Complete wart clearance was achieved in 28.3% of patients using the stronger cream vs. 9.4% with the 2.5% formula.

HIV

- **Vaccine discovery.** In two articles in the journal ***Science***, scientists reported that they found two antibodies to HIV (VRC01 and VRC02) that, in mice, neutralize more than 90% of all strains of the virus. The discovery raises hopes that an HIV vaccine can be developed. And the antibodies might lead to new antiviral drugs. An HIV vaccine has eluded researchers, largely because of the virus's ability to mutate. These antibodies target a part of the HIV envelope that binds to CD4 cells, suggesting that a vaccine targeting that region is possible.
- **Market shifts projected.** ***Datamonitor*** estimates that sales of current antiretroviral drugs will peak in 2012 at

~$12 billion and then decrease ~6% a year. By 2019, half of antiretroviral sales will be for drugs that are only in development today, and use of fixed-dose combinations will increase. The first of the pipeline drugs expected to be approved is Tibotec Pharmaceuticals/Johnson & Johnson's rilpivirine. Use of generic antiretrovirals is expected to double to $1.2 billion by 2019, accounting for 10% of overall sales.

INFINITY PHARMACEUTICALS – grants license

Infinity has licensed the rights to **Intellikine**'s portfolio of inhibitors of the delta and gamma isoforms of phosphoinositide-3-kinase (PI3K), including INK-1197, an oral PI3K expected to start Phase I trials in 2011. The PI3K program will be part of Infinity's existing strategic alliance with Mundipharma International, which is funding the R&D expenses through December 31, 2013, or the start of Phase III, whichever occurs *later*.

Medicaid – state outsourcing problems

States that outsource their Medicaid programs are reporting problems with the companies handling the outsourcing, particularly Centene, according to a ***Washington Post*** report. States are complaining that they are not receiving the services for which they are paying.

For more information see: **www.washingtonpost.com/wp-dyn/content/article/2010/07/07/AR2010070703560.html?sid%3DST2010070705230&sub=AR**

Nicorandil – positive study in hemodialysis patients

A retrospective analysis conducted by Japanese researchers revealed that oral nicorandil reduced the risk of cardiac death by more than 85% among patients on hemodialysis who did not have angiographic evidence of obstructive coronary artery disease. The risk for all-cause mortality among patients taking the potassium channel activator, commonly used to treat angina, was also reduced by 70%. All hemodialysis patients, including those with no evidence of coronary artery disease, are at elevated risk of death, the researchers said. Nicorandil significantly lowered that risk.

Parkinson's disease – brain circuit discovery

In an article in the journal ***Nature***, scientists at the Gladstone Institute of Neurological Disease and Stanford University showed that selective stimulation of the motor planning circuitry in the brain may be important in treating Parkinson's and perhaps other movement disorders, such as Huntington's disease, Tourette's syndrome, obsessive-compulsive disorder, and addiction. By genetically engineering mice and then inserting a fiber optic into the brains of the mice, they proved that specific circuits exert a stop/go effect on movement, and those circuits can be manipulated indefinitely.

In Parkinson's disease, the "stop" pathways were thought to predominate, and the Gladstone/Stanford researchers proved it genetically engineering a molecular "switch" from green algae, which is turned on by blue light, into the brains of the mice, then inserting a very thin fiber optic. They found that by activating the stop pathway, they could mimic Parkinson's disease, and by activating the go pathway, the Parkinson's symptoms disappeared, even in the absence of dopamine.

ROCHE's cobas 4800 HPV test – detects precancerous cervical lesions Pap test misses

Results of the ATHENA trial show that the presence of human papillomavirus (HPV) genotypes 16 and 18 identify women with precancerous cervical lesions missed by routine Papanicolau (Pap) tests. The results emphasize the importance of genotyping in order to accurately detect cervical cancer risk, and women having HPV 16 or 18 should have a colposcopy to further examine the cervix, researchers reported at the 26th International Papillomavirus Conference in Montreal.

The ATHENA trial included more than 47,000 women age 30 years and older who underwent genotyping with the cobas 4800 test system. One in 10 tested positive for HPV genotype 16 or 18. Furthermore, women testing positive for either genotype but who had a normal Pap test were at the same risk of having precancerous cervical lesions as women who tested positive for any of the 14 high-risk HPV types and who had an equivocal Pap test result, meaning that a broad risk of cervical cancer is present.

Shockwave therapy – possible painless therapy for impotence

In a paper in ***European Urology***, Israeli researchers reported that low intensity extra-corporeal shockwave therapy (LI-ESWT), which already is used to treat a number of conditions – from angina to chronic diabetic foot ulcers – can also provide a quick, painless, and effective treatment for impotence. All of the 20 men treated with LI-ESWT improved, and half were able to stop using a PDE-5 inhibitor such as Pfizer's Viagra (sildenafil).

Smoking-cessation medications – California bill would require that insurers cover them

Insurers are opposing a bill in the California Senate (SB-220) which would mandate that they cover FDA-approved smoking-cessation drugs, eliminate co-pays and deductibles, and not require counseling first. Most California insurers currently cover smoking-cessation drugs, but they often restrict access to expensive medications and/or require counseling first. An insurance industry official called the legislation "a good deal for pharmaceutical companies and a bad deal for everybody else." Kaiser Permanente, which offers free smoking-cessation treatment but requires counseling first, opposes the bill.

Statins – no primary prevention benefit

Statin therapy does not appear to reduce the risk of all-cause mortality among high-risk patients in a primary prevention setting, according to a meta-analysis of statin trials published in the June 28 issue of ***Archives of Internal Medicine***. The meta-analysis included 11 clinical trials including 65,229 patients randomized to statin treatment or placebo. Patients were 51-75 years old, 68% were female, and two of the trials specifically enrolled those with diabetes.

Researchers found that the mean rate of all-cause mortality was 11.4 per 1,000 patient-years among placebo patients and 10.7 per 1,000 patient-years among those taking a statin. In addition, researchers found that in these primary prevention patients, there was no significant association between baseline low-density lipoprotein levels and all-cause mortality. The researchers urged caution when "extrapolating the potential benefits of statins on mortality to lower-risk primary prevention populations" and said that even in the high-risk patients studied, the benefit of statins in primary prevention was modest in the short term.

XENOPORT/GLAXOSMITHKLINE's gabapentin enacarbil (XP-13512/GSK-1838262) – failed in migraine

The drug failed in a 30-week, 526-patient, Phase II migraine study. It did meet the primary endpoint – a reduction in the number of migraine headache days – which the company blamed on a unexpectedly high placebo response rate. *The question is whether GSK will now drop the collaboration since the drug also has safety problems in the other indication being sought – restless leg syndrome.*

FDA NEWS

Call for legislation to strengthen FDA recall ability

In an editorial, the ***St. Petersburg Times*** urged Congress to strengthen federal law so the FDA "can properly inspect drug manufacturing plants and force recalls of potentially defective drugs...Americans may be surprised to learn that the FDA can't order a recall, even when it knows drugs are defective." Citing "revelations" in Johnson & Johnson's recent recall of children's over-the-counter medicines, the paper said the FDA needs "the manpower and regulatory muscle" to check drug making plants and pull "dangerous" drugs off the market.

FDA to conduct electronic records inspections

The FDA announced it "soon" will begin a series of "focused" inspections to evaluate the drug industry's compliance with 21 CFR 11 (Part 11) requirements relating to electronic records and electronic signatures. The requirement was intended to permit wide use of electronic technology, and the FDA will be checking to see that industry is following the guidance that was issued.

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Upcoming FDA Advisory Committees of Interest ***(items in red are new since last week)***

Date	Topic	Committee
	July 2010	
July 13-14	**GlaxoSmithKline's Avandia** (rosiglitazone) cardiovascular safety – and to a lesser extent the safety of **Takeda's Actos** (pioglitazone)	Joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee ***and*** the Drug Safety and Risk Management Advisory Committee
July 15	**Vivus's diet drug Qnexa** (phentermine + topiramate)	Endocrinologic and Metabolic Drugs Advisory Committee
July 19-20	**Oversight of laboratory-developed tests**, especially genetic tests	Public meeting
July 20	**Roche/Genentech's Avastin** (bevacizumab) – two supplemental BLAs for naïve metastatic HER2-negative breast cancer	Oncologic Drugs Advisory Committee (ODAC)
July 22-23	**REMS for long-acting opioids**	Joint meeting of the Anesthetic and Life Support Drugs Advisory Committee ***and*** the Drug Safety and Risk Management Advisory Committee
July 27	**Medtronic's Amplify rhBMP-2 Matrix**	Orthopedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee
July 27-28	Meeting to obtain input on issues and challenges associated with the development and implementation of risk evaluation and mitigation strategies (**REMS**)	Public hearing
July 28	**AstraZeneca's Brilinta** (ticagrelor)	Cardiovascular and Renal Drugs Advisory Committee
July 30	**Glaukos's iStent Trabecular Micro-Bypass Stent** for treating open-angle glaucoma during cataract surgery	Ophthalmic Devices Advisory Committee
	August 2010	
August 11	**Valeant/GSK's Potiga** (ezogabine, formerly retigabine) for epilepsy	Peripheral and Central Nervous System Drugs Advisory Committee
August 19	**Lilly's Cymbalta** (duloxetine) for chronic pain	Anesthetic and Life Support Drugs Advisory Committee
August 20	**Jazz Pharmaceuticals' Xyrem** (sodium oxybate, JZP-6) for fibromyalgia	Arthritis Advisory Committee joint meeting with the Drug Safety and Risk Management Advisory Committee
August 26	**Mela Sciences' MelaFind,** an optical device for melanoma detection	General and Plastic Surgery Devices Advisory Committee
	September 2010	
September 7	**Forest/Cerexa's ceftaroline fosamil injection** for infection	Anti-Infective Drugs Advisory Committee
September 16	**Arena Pharmaceuticals' locaserin** diet drug	Endocrinologic and Metabolic Drugs Advisory Committee
September 17 (not confirmed)	**Boehringer Ingelheim's Pradaxa** (dabigatran)	Cardiovascular and Renal Drugs Advisory Committee