TRENDS-in-MEDICINE

April 1, 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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NOTE: For full coverage of the American College of Cardiology meeting and the FDA's Endocrinologic and Metabolic Drugs Advisory Committee meeting on cardiovascular study requirements for obesity drugs, subscribe to ***Trends-in-Medicine***.

SHORT TAKES

- **ALMIRALL and FOREST LABORATORIES' aclidinium bromide –** The FDA extended its review of this inhaled therapy for chronic obstructive pulmonary disease (COPD) by three months, making the new PDUFA date July 30, 2012.

- **ANGELINI PHARMA's bindarit –** A small study presented at the American College of Cardiology meeting found that this oral anti-inflammatory compound significantly improves six-month angiographic outcomes in stable coronary artery disease patients who receive a bare metal stent, reducing in-stent late loss vs. placebo with no increase in adverse events.

- **BIOMET** agreed to pay the federal government more than $22 million to settle charges by the Department of Justice (DOJ) and the Securities and Exchange Commission (SEC) that it violated the Foreign Corrupt Practices Act by making various improper payments or bribes from 2000 to 2008 to healthcare providers in Argentina, Brazil, and China to get business.

- **BIONOMICS' BNC-105 –** The FDA gave the company approval to initiate a Phase I/II trial of this investigational vascular disruption agent to treat ovarian cancer. The trial is expected to start in 2Q12.

- **BRISTOL-MYERS SQUIBB's Yervoy (ipilimumab) –** A small Phase II trial published in ***The Lancet Oncology*** found that this melanoma drug may help patients with brain metastases. Usually patients are excluded from clinical trials once they have brain mets, but these researchers suggested that should be re-thought.

- **CETERO RESEARCH**, a contract research firm that does early-phase clinical research and bioanalytics for a number of pharmas, filed Chapter 11 bankruptcy, saying the FDA charge that it falsified documents caused its "liquidity position to become severely constrained."

- **CHELSEA THERAPEUTICS' Northera (droxidopa) –** The FDA rejected this hypotension therapy despite a 7-4 vote by the Cardiovascular and Renal Drugs Advisory Committee in favor of approval. The FDA suggested the company conduct another study to prove the treatment works well for 2-3 months and said the device probably will carry a boxed warning about supine hypertension if it is approved.

- **Cystic fibrosis** – A 6-patient, 10-year study published in the ***Proceedings of the National Academy of Sciences*** found that antibiotics can prolong survival but that the drugs also help treatment-resistant bacteria thrive in the patients' lungs. The study suggests, but does not prove, that the current practice of aggressive antibiotic treatment ("carpet bombing") may not always be the best approach. The researchers said that maintaining a more diverse range of bacteria in the lungs may help keep the most dangerous strains in check and help some patients stay healthy longer.

- **Electronic health records (EHRs)** – A ***Healthcare IT News*** survey of its readers found that 31% believe meeting the requirements of Stage 2 (data exchange) will be more difficult than they had expected.

- **ENDOCYTE's vintafolide (EC-145)** – A study presented at the Society of Gynecologic Oncology meeting found that this investigational folate conjugate nearly doubled progression-free survival in patients with platinum-resistant ovarian cancer vs. pegylated liposomal doxorubicin (PLD) alone (5.0 months vs. 2.7 months).

- **FOREST LABORATORIES' Celexa (citalopram)** – The FDA updated the warning about potentially fatal arrhythmias with this antidepressant. Instead of contra-indicating it in patients at high risk of certain pre-existing heart conditions (e.g., congestive heart failure), the FDA modified the warning, saying that for some of these patients the benefits may outweigh the risks. The new label also advises that a lower dose should be used in people ≥age 60.

- **HORIZON DISCOVERY's HORIZON DIAGNOSTICS** division (HDx) signed a strategic partnership agreement with the European Molecular Genetics Quality Network (EMQN) under which HDx will provide genetically defined human cell-line reference standards for distribution to molecular diagnostic laboratories around the world to help ensure sensitivity and reproducibility of diagnostic assays. The HDx materials will contain known frequencies of mutations that currently guide the prescription of cancer therapies, particularly melanoma, colorectal, and lung cancer.

- **MAP PHARMACEUTICALS' Levadex (dihydroergotamine mesylate, MAP-0004)** – The FDA rejected this inhaled therapy for acute migraine headaches. The company said the Agency did not request additional studies or express concern about safety or efficacy. Rather, the problems appear to be the inhaler device and the third-party manufacturer.

- **MERCK's Zetia (ezetimibe) and Vytorin (ezetimibe + simvastatin)** – A pre-specified analysis of the 18,000-patient IMPROVE-IT outcomes trial, testing these two cholesterol-lowering drugs vs. statins, found no problems. The trial will continue for at least another nine months, at which point another pre-planned analysis will occur. The trial will be completed in June 2013.

- **MYRIAD GENETICS** said it agreed to perform BRCA1 and BRCA2 genetic mutation testing for **Teva's Cephalon** subsidiary.

- **NORDION's TheraSphere (yttrium-90 microspheres)** – A 537-patient retrospective study presented at the Society of Surgical Oncology meeting found treating hepatic tumors with yttrium-90 radioembolization increased median survival >6 months (to 10.5 months from 4.0 months) with conventional therapy.

- **SANOFI/GENZYME and ISIS' Kynamro (mipomersen sodium)** was submitted to the FDA for approval to treat homozygous familial hypercholesterolemia, a genetic disorder characterized by high cholesterol.

- **Statins** – A Canadian population-based study published in ***Arthritis Care & Research*** found that rheumatoid arthritis patients who stop their statin therapy have a 60% increased risk of cardiovascular death and a 79% increase in the risk from all-cause death.

- **THRESHOLD PHARMACEUTICALS' TH-302** was granted orphan drug status for treating soft tissue sarcoma. A Phase III trial is ongoing.

NEWS IN BRIEF

ALLERGAN's Botox (onabotulinumtoxinA) – positive results in OAB and an FDA submission

Botox was submitted to the FDA and to European regulators for a supplemental biologics-license application to treat adults with overactive bladder (OAB) who do not benefit from standard anticholinergic therapy. Allergan also reported top-line results for a Phase III study of Botox in OAB, showing a statistically significant decrease in daily incontinence episodes vs. placebo ($p<0.001$). Adverse events of interest were: urinary tract infection (UTI) 15%-20% and urinary retention 5%-6%.

GLAXOSMITHKLINE's Pandemrix – linked to narcolepsy

Two studies published in ***PLoS ONE*** linked this H1N1 pandemic flu vaccine to a sudden increase in narcolepsy cases in children in Finland in 2010. The first study found a 17-fold increase in the rate of narcolepsy among kids and teens <age 17 after the vaccinations. The study found that the incidence of narcolepsy was 3-fold higher for vaccinated individuals than

for the unvaccinated. People age ≥20 were not affected. The researchers speculated that the vaccine was some sort of a "trigger" in children. The AS03-adjuvanted Pandemrix was the only vaccine used in Finland during the pandemic.

Metal-on-metal hip implants – FDA advisory committee to review

The FDA's Orthopaedic and Rehabilitation Devices Advisory Committee will meet on June 27-28, 2012, to help the Agency decide whether it should impose more rigorous testing and premarket review requirements for these products. In May 2011 the FDA ordered manufacturers of metal-on-metal hip systems to conduct postmarketing safety studies, but a recent study that found an increased failure rate with metal-on-metal hips that have large-diameter femoral heads has raised the level of concern at the FDA. Topics to be discussed at the panel are: Failure rates and modes, metal ion testing, imaging methods, local and systemic complications, patient risk factors, and considerations for follow-up after surgery.

PFIZER

- **Aricept (donepezil).** An article published in the ***British Medical Journal (BMJ)*** strongly criticized a new 23 mg dose of this Alzheimer's drug, saying it will do little to help most patients and will increase adverse events for some. Steven Woloshin, MD, and Lisa Schwartz, MD, primary care physicians from Dartmouth Medical College, said the dose is "no more effective on the whole than the disappointing ones already on the market but is more likely to cause gastrointestinal problems." They charged that the new formulation "was devised to serve commercial objectives… and was approved despite a poor showing in company-sponsored tests."
- **Lyrica (pregabalin).** A study, sponsored by Pfizer and published in ***Arthritis Care & Research***, found that Lyrica can help fibromyalgia patients sleep better.

ROCHE's trastuzumab emtansine (T-DM1) – positive Phase III results

Roche announced positive Phase III results from the international, randomized, open-label EMILIA trial in 991 women with HER2+ metastatic breast cancer who had previously been treated with **Herceptin** (trastuzumab) + a taxane (chemotherapy). In the study, T-DM1 met the first of two co-primary endpoints, significantly extended progression-free survival (PFS) vs. **GlaxoSmithKline's Tykerb** (lapatinib) + **Xeloda** (capecitabine). The results for overall survival, the other co-primary endpoint, are not yet available. Roche said it plans to submit T-DM1 in Europe and to the FDA this year. *A breast cancer expert said, "This confirmed it will make it and be approved."*

SALIX PHARMACEUTICALS' Xifaxan (rifaximin) – news in two conditions

- **Irritable bowel syndrome (IBS).** A meta-analysis published in the ***American Journal of Medicine*** concluded that there is not a significant risk of adverse events with this antibiotic when used to treat IBS. In fact, the study found that Xifaxan and **Takeda's Amitiza** (lubiprostone), another IBS therapy, have the lowest level of harmful side effects of all the well-studied drug therapies for IBS. The Cedars-Sinai Medical Center researchers reviewed 26 randomized, double-blind, placebo-controlled trials of tricyclic antidepressants, the 5-HT_3 antagonist alosetron (Prometheus Laboratories' Lotronex, originally a Glaxo-SmithKline drug), Xifaxan, lubiprostone (a fatty acid derivative stool softener), and selective serotonin reuptake inhibitors.
- **Hepatic encephalopathy (HE).** A study published in ***Hepatology***, a journal of the American Association for the Study of Liver Diseases (AASLD), found that detecting and then treating minimal hepatic encephalopathy (MHE) prevents car accidents. The researchers reported that using the inhibitor control test to identify MHE followed by treatment with lactulose and/or Xifaxan was the most cost-effective approach, preventing the most car accidents and reducing societal costs by ≤$3.6 million over five years. The researchers found that the cost of each motor vehicle accident prevented by diagnosing MHE was:
  - $24,454 with the inhibitory control test.
  - $25,470 with standard psychometric tests.
  - $30,469 with presumptive treatment.
  - $33,742 with a neuropsychological exam.

  An accompanying editorial noted that driving errors account for 71%-98% of all motor vehicle accidents and suggested that this makes assessing driving ability crucial for patients with MHE.

REGULATORY NEWS

FDA may regulate some cosmeceuticals

Michael Landa, director of the FDA's Center for Food Safety and Applied Nutrition, told a House subcommittee that the FDA might begin regulating some cosmetics – those with active ingredients such as retinol and peptides – as drugs. He

said those products straddle the line between beauty products and drugs.

FDA issues guidance clarifying PMA and de novo device reviews

The FDA released new guidance – Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications – intended to clarify the process it uses to review medical devices for premarket approval or de novo classification. The guidance, which will take effect on May 1, also will provide reviewers with uniform and consistent guidelines for assessing risk:benefit.

The guidance says reviewers look at all the benefits a device claims, including type of benefit, magnitude of benefit, the probability of patients getting a benefit, and the length of the benefit. Reviewers also look at risks, including severity, types, numbers, and rates of adverse events, as well as the probability and likely duration of an adverse event.

FDA pilot program to reduce inspections

On June 5, 2012, the FDA will start a new program to allow medtech firms to skip reinspections for a year, in certain situations, if they have already been audited by a Global Harmonization Task Force founding member. To join the program, companies must submit the report from their last audit within 90 days of the audit's last day.

FDA says alarm fatigue part of new device approvals

The FDA said it will provide more training for its staff about the safety issues of alarm fatigue, to ensure they consider it when evaluating applications for medical devices in hospitals. They also will be instructed to consider whether alarms on new devices actually provide information important to patient care.

GAO criticizes timeframe for FDA device approvals

The Government Accountability Office (GAO) issued a report that found that the FDA has not consistently met its performance objectives for premarket approval applications (PMAs), though it did achieve most of the 510(k) clearance goals. The GAO also found that the time it takes for the FDA to issue a final decision on either a PMA or a 510(k) application increased between FY2003 and FY2010.

FDA approvals/clearances

- **AFFYMAX and TAKEDA's Omontys** (peginesatide, formerly known as **Hematide**), a once-monthly injectable erythropoiesis-stimulating agent (ESA), was approved to treat anemia in adult dialysis patients.
- **AVLOQ's Avloq HTLV-I/II Microelisa System**, a test to screen a donor's blood and blood components for antibodies to viruses, including antibodies to human T-lymphotropic virus Type I and II (HTLV-I and -II), was approved.
- **BECTON DICKINSON's BD MAX GBS Assay**, an *in vitro* diagnostic test to detect group B *Streptococcus* in Lim broth cultures, was cleared.
- **INTEGRA LIFESCIENCES' Jarit Take-Apart Laparoscopic instruments** were granted 510(k) clearance.
- **JOHNSON & JOHNSON/TIBOTEC's Intelence (etravirine, TMC-125)** – The FDA expanded the indication for this HIV drug to pediatric patients age ≥6 in combination with other antiretroviral drugs and approved a new 25 mg dose.
- **MERIT MEDICAL's 30-60um QuadraSphere Microspheres**, which remove oxygen and blood in tumors by obstructing vessels linked to them, was granted 510(k) clearance.
- **ST. JUDE MEDICAL's Aeris and Certus guidewires** – next-generation additions to the company's **PressureWire** fractional flow reserve system for treating blocked arteries – were cleared.
- **TEVA's QNASL (beclomethasone dipropionate)**, a dry powder spray corticosteroid for seasonal and year-round allergies, was approved. The company plans to make it available in April 2012.
- **ZOLL MEDICAL's X Series monitor/defibrillator**, a lighter-weight and smaller device designed for EMS use, received 510(k) clearance.

FDA recalls/warnings

- **LUCERO MEDICAL's Enduramesh** – The FDA sent the company a warning letter about documentation issues and quality violations at its facilities in Ohio, where this device used in spinal fusion procedures is manufactured. The FDA also said the company had misbranded product.
- **SUN PHARMACEUTICAL INDUSTRIES** recalled 155,000 bottles of an ophthalmic solution after impurities were found.

- **TEVA and EAGLE PHARMACEUTICALS** withdrew 7,260 bottles of flutamide, produced at a **Cipla** plant in India, because some bottles contained imatinib mesylate (**Novartis' Gleevec**).

European regulatory actions

- **AMYLIN PHARMACEUTICALS' Byetta (exenatide)** – The European Medicines Agency (EMA) approved an expanded indication for this Type 2 diabetes drug for use with or without concomitant therapy – e.g., metformin, **Takeda's Actos** (pioglitazone), etc. – in patients not controlled with just insulin.
- **ARENA PHARMACEUTICALS' Lorqess (lorcaserin)** was accepted for review by the EMA. The FDA's Endocrinologic and Metabolic Drugs Advisory Committee will review this diet drug on May 10, 2012, and the PDUFA date is June 27, 2012.
- **QUIDEL's AmpliVue**, a hand-held molecular diagnostic assay for *C. difficile*, received a CE Mark.

Regulatory news from other countries

Canada: Health Canada accelerated approval of **Omega Laboratories'** rocuronium bromide, a muscle relaxant, and **Accord Healthcare's** ondansetron, an anti-nausea drug, to ease a nationwide shortage.

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 2	Types of consumer studies needed to assess proper use of a **MedKit containing doxycycline** in the event of **anthrax exposure**	FDA's Anti-Infective Drugs Advisory Committee meeting jointly with the Non-Prescription Drugs Advisory Committee
April 3-4	**Pneumonic plague** discussion: animal models, ciprofloxacin efficacy and safety, **Johnson & Johnson's Leaquin** (levofloxacin) safety and efficacy	FDA's Anti-Infective Drugs Advisory Committee
April 5	**Astellas' Betanis** (mirabegron), a beta-3-adrenoceptor agonist to treat overactive bladder (OAB)	FDA's Reproductive Health Drugs Advisory Committee
April 11	**U-Systems' Automated Breast Ultrasound (ABUS) scanning device** for breast cancer detection in asymptomatic dense-breasted women	FDA's Radiological Devices Advisory Committee
April 12	Possible reclassification of **breast transilluminators**, which are currently pre-amendment Class III devices, and **blood irradiators**	FDA's Radiological Devices Advisory Committee
April 17	**Vivus' Qnexa** (phentermine + topiramate) for weight loss	PDUFA date for resubmission
April 18	Use of minimal residual disease as a biomarker for evaluating new drugs to treat **acute lymphoblastic leukemia (ALL)**	FDA public workshop in conjunction with the American Society of Clinical Oncology (ASCO)
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	**Boston Scientific/Cameron Health's S-ICD**, a lead-less implantable cardioverter defibrillator	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
	May 2012	
May 1	**Protalix Biotherapeutics' Uplyso** (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 6	**GlaxoSmithKline's Votrient** (pazopanib) to treat sarcoma	PDUFA date
May 8	**Regeneron Pharmaceuticals' Arcalyst** (rilonacept), an interleukin-1 inhibitor to prevent gout flares during initiaton of uric acid-lowering therapy	FDA's Arthritis Advisory Committee
May 9	**Pfizer's tofacitinib**, an oral JAK inhibitor, to treat rheumatoid arthritis	FDA's Arthritis Advisory Committee
May 10	**Gilead Sciences' Truvada** (emtricitabine + tenofovir) for HIV prevention	FDA's Antiviral Drugs Advisory Committee
May 10	**Arena Pharmaceuticals and Eisai's Lorqess** (lorcaserin) for obesity	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
May 10-11	**Trial design for obesity devices** (balloons, suture devices, bands, space-occupying devices, etc.), studies, and discussion of what is clinically meaningful weight loss	FDA's Gastroenterology and Urology Devices Advisory Committee
May 11	**Gilead Sciences' Quad** (emtricitabine + tenofovir + elvitegravir + cobicistat) for HIV	FDA's Antiviral Drugs Advisory Committee
May 13	**Talon Therapeutics' Marqibo** (vincristine sulfate liposomes injection) for Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL)	PDUFA date
May 16-17	**Natural history studies of rare diseases:** meeting the needs of drug development and research	FDA workshop
May 22-23 (?)	**Bristol-Myers Squibb's Eliquis** (apixaban), an anticoagulant for prevention of stroke in AFib, and **Johnson & Johnson's Xarelto** (rivaroxaban), an anticoagulant for a supplemental indication in acute coronary syndrome (ACS)	FDA's Cardiovascular and Renal Drugs Advisory Committee (*Neither of these is official yet. It may be that Eliquis is May 22 and Xarelto May 23, but this is not certain.)*
May 24	**St. Jude Medical's Amplatzer** and **Gore's Helex ASD Occluder** for atrial septal defect closure – discussion of current safety and effectiveness for these devices, first approved in 2001 and 2006, respectively	FDA's Circulatory System Devices Advisory Committee
May 30-31	Discussion of **analgesic treatment of chronic pain** – mechanisms, epidemiology, new data on opioid efficacy, etc.	FDA public workshop

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Date	**Topic**	**Committee/Event**
	June 2012	
June 5	**Salix Pharmaceuticals' crofelemer** for HIV-related diarrhea	PDUFA date
June 5	**Merck/Ariad Pharmaceuticals' Taltorvic** (ridaforolimus) for sarcoma	PDUFA date
June 8	**Forest Laboratories and Ironwood Pharmaceuticals' linaclotide** for IBS-C	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) for pain	PDUFA date
June 26	**Edwards Lifesciences' Sapien** transcatheter aortic valve	CMS final NCD expected
June 27	**Arena Pharmaceuticals and Eisai's Lorqess** (lorcaserin) for obesity	PDUFA date
June 27-28	Risk:benefit of **metal-on-metal hip replacement** and **resurfacing**	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
June 28	**Bristol-Myers Squibb's Eliquis** (apixaban), an anticoagulant for the prevention of stroke in AFib	PDUFA date
June 29	**Astellas Pharma's mirabegron** for treatment of overactive bladder	PDUFA date
	Other 2012	
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
July 30	**Almirall and Forest Laboratories' aclidinium** inhaled therapy for chronic obstructive pulmonary disease (COPD)	***New*** 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
October 29	**Cornerstone Therapeutics' CRTX-800** to treat hyponatremia	PDUFA date