TRENDS-in-MEDICINE

June 3, 2012

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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: Subscribe to ***Trends-in-Medicine*** for full coverage of the American Society of Clinical Oncology (ASCO) meeting.

SHORT TAKES

- **ACORDA THERAPEUTICS** received a warning letter from the FDA for persistent late reporting of adverse drug reactions – which include things like memory impairment, hypersensitivity, acute fulminant hepatitis, arrhythmia, irregular heartbeat, and death.

- **ALKERMES' ALKS-37 –** The company said it is giving up on this investigational drug to treat opioid-induced constipation but may license it to another company.

- **ALNYLAM PHARMACEUTICALS' ALN-RSV01** missed the primary endpoint in a Phase II trial for respiratory syncytial virus infection, failing to reduce bronchiolitis obliterans syndrome.

- **GLAXOSMITHKLINE's Promacta/Revolade (eltrombopag) –** The company submitted this drug to the FDA and European regulators for an expanded indication to treat low platelet counts in hepatitis C patients.

- **LUNDBECK's Lu AE-58054 –** The company reported that a 278-patient Phase II trial met its primary endpoint. When given in combination with **Pfizer's Aricept** (donepezil), Lu AE-58054 improved cognition in Alzheimer's patients and was well tolerated.

- **NEVRO's Senza High-Frequency Spinal Cord Stimulation System –** The FDA gave the company permission to begin a trial of this chronic pain treatment in ~300 patients.

- **OSIRIS THERAPEUTICS' Grafix –** The Centers for Medicare and Medicaid Services (CMS) said it is assigning transitional reimbursement codes for this mesenchymal skin therapy for acute and chronic wounds, effective July 1, 2012, and permanent Q-codes may follow in January 2013.

- **REPROS THERAPEUTICS' Proellex (telapristone) –** The company said it has to do a safety analysis of existing data before it can resume human testing of this investigational oral treatment for menstrual bleeding associated with uterine fibroids and for endometriosis.

- **RXI PHARMACEUTICALS' RXI-109 –** The FDA gave the company permission to begin Phase I trials of this RNAi compound that selectively targets Connective Tissue Growth Factor (CTGF) to reduce scarring from surgery.

- **ST. JUDE MEDICAL's Amplatzer –** The FDA's Circulatory System Devices Advisory Committee reviewed the safety of this septal occluder and recommended the FDA analyze existing data for the device, which has been on the market since 2001. The panel was concerned about rare but serious adverse events – erosion of cardiac structures and cardiac perforations. The panel basically wants the FDA and St. Jude to take a broad view in the re-analysis, focusing not just on anatomical factors.

- **SANOFI/GENZYME and ISIS PHARMACEUTICALS' Kynamro (mipomersen sodium) –** Genzyme said the FDA has accepted its submission of this drug to treat a rare, genetic form of extremely high cholesterol, but the FDA did not grant accelerated approval.

- **ZOGENIX's Relday (risperidone) –** The company submitted an investigational new drug (IND) application to the FDA to start clinical trials of this once-monthly antipsychotic. Relday uses a proprietary formulation of risperidone, administered via the company's **DosePro** needle-free subcutaneous delivery system. The trials are expected to start in 2H12.

NEWS IN BRIEF

EXELIXIS' cabozantinib

- **Phase III trial must show mortality benefit.** The company announced initiation of the pivotal double-blind, placebo-controlled, international Phase III COMET-1 trial in ~960 metastatic castration-resistant prostate cancer (mCRPC) patients who progressed after treatment with docetaxel and either **Johnson & Johnson's Zytiga** (abiraterone) or **Medivation/Astellas' Enzalutamide** (MDV-3100) and who have bone metastases. The results are expected in 1H14. The trial is powered to show a 25% reduction in the risk of death (HR=0.75), and the final analysis will be event-driven, with 578 events required. A single interim analysis is planned after 387 events. The secondary endpoint is bone scan response as assessed by an independent radiology facility (IRF).

- **A new drug application (NDA) was filed** to treat progressive, unresectable, locally advanced, or metastatic medullary thyroid cancer, based on the EXAM study, which met the primary endpoint, showing an improvement in progression-free survival (PFS) vs. placebo. It has fast track status, and the company requested priority review.

GILEAD SCIENCES and BRISTOL-MYERS SQUIBB – on again/off again romance

In April 2012 it looked like Gilead wanted a divorce from BMS, preferring to go it alone in developing an all-oral therapy for hepatitis C. Then, Gilead officials denied that, so it looked like the two companies were reconciling and would take the combination of Gilead's GS-7977 and BMS's daclatasvir into Phase III. But now it appears Gilead isn't very interested in a reconciliation since BMS CEO Lamberto Andreotti had to go public with a plea for Gilead to do the combination trial in the interest of patients.

Home telemonitoring – did not cut hospitalizations/ER visits

A Mayo Clinic study of 205 elderly (about age 80) comorbid patients, published in ***Archives of Internal Medicine***, found that using devices in the home to measure and transmit information about blood pressure and other values did not reduce hospitalizations and emergency department visits. Paul Takahashi, MD, MPH, an associate professor of medicine at the Mayo Clinic, said, "We…thought using a monitoring system and taking measurements every day would help these patients avoid the hospital. Unfortunately, we did not find that… Maybe the sickest population is not the right population. Maybe it's those not quite as ill for whom you can make changes in treatments that will make a real difference."

JOHNSON & JOHNSON

- **Canagliflozin.** The drug was submitted to the FDA as a QD pill to treat Type 2 diabetes.

- **Prezista (darunavir).** The FDA rejected J&J/Janssen's request for approval of a once-daily, higher dose (800 mg QD) of this protease inhibitor to treat HIV, issuing a complete response letter asking for more information. A 400 mg BID dose already is approved.

- **Warning letter.** Just when the noise about almost weekly drug recalls had quieted down, the FDA warned J&J that its **McNeil** division has not been properly investigating consumer complaints about an odd consistency in its K-Y liquibeads vaginal moisturizer and a case of toxic shock syndrome related to an OB tampon. The FDA also said J&J failed to get FDA approval of a change to the K-Y product.

REGENERON and SANOFI's REGN-727 – positive Phase II results

A 77-patient, 12-week, Phase II study presented at the European Atherosclerosis Society Congress in Milan, Italy, and simultaneously published in ***The Lancet*** found that this PCSK9 inhibitor effectively lowers LDL in adults with an inherited condition that causes high cholesterol levels who did not respond to statin therapy. REGN-727 reduced LDL by 28%-67.9% (depending on the dose) vs. 10.7% for placebo. A Phase III trial is expected to start this month.

Stem cells – possibly not so safe

A study published in the ***Journal of the American College of Cardiology*** might put the brakes on stem cell treatments for myocardial infarction (MI) patients. The researchers suggested that using a patient's own stem cells to rejuvenate the heart after an MI could be dangerous. They detected several circulating micro-RNAs from bone marrow-derived mononuclear cells in stem cells from MI patients but not in stem cells taken from healthy volunteers. *In vitro* experiments showed that these particular micro-RNAs are associated with reduced survival of the stem cells. The researchers suggested that this might explain why cardiac stem cell therapy has had mixed results so far.

TAKEDA's Actos (pioglitazone) – more data on a link to bladder cancer

A study published in ***BMJ*** linked this thiazolidinedione to an increased risk of bladder cancer. Investigators collected data on ~116,000 diabetics from a U.K. database and found that Type 2 diabetics who were ever treated with Actos had an 83% higher risk of bladder cancer vs. never users. They concluded this was a drug-specific effect, not a class effect, because patients taking **GlaxoSmithKline's Avandia** (rosiglitazone) did not have an elevated risk.

VERTEX PHARMACEUTICALS

- **Incivek (telaprevir).** The FDA told Vertex not to distribute promotional materials that the Agency said overstate the benefits and understate the risks of this hepatitis C drug. However, Vertex said the materials in question had not been distributed yet.
- **Kalydeco (ivacaftor) + VX-809 –** The company revised downward the efficacy of this combination in improving lung function in a pre-planned interim analysis of an ongoing Phase II study in 48 adult cystic fibrosis (CF) patients with two copies of the F508del gene mutation, which is the most common CF mutation. New p-values were not given. Vertex said the error was due to a "misinterpretation" between the company and the outside statistical vendor on the type of responder analysis performed. *This was supposed to be the good news out of a trial that missed the primary endpoint.*

  Vertex also provided additional data from the interim analysis, reporting that patients on the combination showed ≥8.5% absolute improvement in lung function vs. placebo.

Efficacy of Kalydeco + VX-809 in Cystic Fibrosis		
Measurement	**Revised**	**Original**
Primary endpoint: Improvement in FEV_1 **≥5%** at Day 56	35%	46%
Primary endpoint: Improvement in FEV_1 **≥10%** at Day 56	19%	30%

REGULATORY NEWS

FDA backs surrogate endpoint for breast cancer trials

The FDA issued draft guidance on the use of pathologic complete response (pCR) to support accelerated approval of drugs for neoadjuvant therapy of high-risk, early-stage breast cancer.

FDA investigating allergic reactions to drugs

The FDA's Center for Drug Evaluation and Research (CDER) has a team of researchers studying allergic reactions to drugs. In particular, they have been studying immune reactions to two HIV drugs – **GlaxoSmithKline's Ziagen** (abacavir) and **Epzicom** (abacavir + lamivudine) – to see if they can identify which patients are at highest risk, but these are not the only drugs being studied. The Agency hopes that the research will help it evaluate the safety of new medications.

FDA public workshop on long-term opioid use

The FDA held a two-day public meeting to discuss the ***efficacy*** (not the safety) of long-term use of opioids to treat non-cancer chronic pain. And this may be just the first public meeting in the FDA's effort to decide if long-term opioid use for non-cancer pain is appropriate.

The FDA's Douglas Throckmorton, MD, deputy director for regulatory programs at CDER, said increasing opioid use "has resulted in a clearly unacceptable increase in addiction, overdose, and death."

While there were no definitive decisions out of the meeting, pain specialists and researchers seemed to agree that there is little evidence to support the long-term use of opioids for chronic pain, except perhaps in patients not able to be helped

with other analgesics and who have a low likelihood of addiction. There was general agreement that more study is needed.

Findings presented at the workshop included:

- Opioids beat placebo in reducing knee or hip pain and provide a "modest" improvement in function.
- Back pain patients who took opioids for more than a week were twice as likely to still be out of work in a year vs. patients who took them for a shorter time, suggesting long-term opioid use does not improve functionality.
- There is no difference in effectiveness between high- and low-dose opioids.
- About half of patients in opioid trials stopped taking the drug after 18-24 months.
- There are no good estimates of how many patients do well on opioids for management of long-term pain.
- Opioids are rarely beneficial for mechanical pain but are likely to be effective for neuropathic pain after other therapies have failed.

Pam Horn, MD, of CDER's Division of Anesthesia, Analgesia, and Addiction Products, said most practice guidelines agree that there is evidence to support the efficacy of opioids in treating chronic pain but that they must be prescribed to the appropriate patient.

FDA approvals/clearances

- **BOSTON SCIENTIFIC's CRE Wireguided Balloon Dilator** was approved for endoscopic dilation of the sphincter of oddi – a valve that controls the flow of digestive juices – following sphincterotomy (i.e., removing large bile duct stones).
- **MEDIGUS' SRS** endoscope, used to treat gastroesophageal reflux disease (GERD), was cleared for use.
- **TELEFLEX's Arrow FlexTip Plus** closed-tip, multiport epidural catheter was given 510(k) clearance.
- **VIEWRAY's ViewRay System**, an MRI-guided radiation therapy device for treating cancer patients, was granted 510(k) clearance.

FDA recalls/warnings

TEVA's Adderall (dextroamphetamine+amphetamine) – The FDA issued a warning that a counterfeit version of the 30 mg dose of this attention-deficit/hyperactivity disorder (ADHD) drug is being sold online. The fake drug contains acetaminophen and tramadol, not the active ingredients in Adderall. The counterfeit pills are white; the real ones are peach colored.

European regulatory actions

- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran)** – The European Medicines Agency (EMA) said patients and physicians need better (stronger) guidance on how to prevent bleeding (especially fatal bleeding) when using this anticoagulant, but the EMA said the benefits still outweigh the risks.
- **EISAI's Fycompa (perampanel)** – The EMA's Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion to treat partial-onset seizure in epilepsy.
- **LILLY and BOEHRINGER INGELHEIM's Jentadueto (metformin + linagliptin)** – The EMA's CHMP recommended approval of this combination treatment for Type 2 diabetes. The European Commission will make a final determination in the next two months.
- **PFIZER's Inlyta (axitinib)** – CHMP recommended that the EMA approve this drug to treat adults with advanced renal cell carcinoma who do not respond to Pfizer's **Sutent** (sunitinib) or cytokines.
- **ROCHE's MabThera (rituximab, sold as Rituxan in the U.S.)** – The EMA said this cancer drug is safe to use despite a report of *Leptospira licerasiae* contamination at a U.S. plant, saying the contaminant was not detected at later stages of production, and all contaminated material was discarded.
- **VERTEX PHARMACEUTICALS' Kalydeco (ivacaftor)** – The EMA recommended the European Commission approve this for use in cystic fibrosis (CF) patients with the G551D mutation, which is a very small percentage of all CF patients.
- **Medical device oversight** –The U.K.'s Medicines and Healthcare products Regulatory Agency said it opposes a proposal to subject certain high-risk medical devices sold in Europe to premarket review in addition to the oversight already required, saying that might "muddy the water" as to where responsibility lies for premarket scrutiny and would risk reducing the responsibility of a Notified Body to undertake its review properly.

Regulatory news from other countries

Japan: **GENMAB's Arzerra (ofatumumab)** was submitted to the Japanese Ministry of Health, Labour, and Welfare as a second-line therapy for chronic lymphocytic leukemia (CLL).

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	June 2012	
June 5	**Merck/Ariad Pharmaceuticals' Taltorvic** (ridaforolimus) for sarcoma	PDUFA date
June 8	**Roche/Genentech's pertuzumab** in HER2+ advanced breast cancer	PDUFA date
June 13	**Edwards Lifesciences' Sapien** transcatheter aortic valve repair (TAVR), an expanded indication for high-risk, operable patients	FDA's Circulatory System Devices Advisory Committee
June 15	**Gilead Sciences' Truvada** (emtricitabine + tenofovir) for HIV prevention	PDUFA date
June 20	**Onyx Pharmaceuticals' carfilzomib**, a treatment for relapsed and refractory multiple myeloma	FDA's Oncologic Drugs Advisory Committee (ODAC)
June 21	**Dune Medical Devices' MarginProbe System**, which uses electromagnetic waves to characterize human tissue and provides intraoperative information on a malignancy of the surface of *ex vivo* lumpectomy specimens	FDA's General and Plastic Surgery Devices Advisory Committee
June 21	**Repligen's RG-1068**, an imaging agent to help identify abnormalities in pancreatic ducts	PDUFA date
June 25	**QRxPharma's MoxDuo** (morphine + oxycodone) for pain	PDUFA date
June 27	**Arena Pharmaceuticals and Eisai's Lorqess** (lorcaserin) for obesity	PDUFA date
June 27	**Onyx Pharmaceuticals' carfilzomib**, a treatment for relapsed and refractory multiple myeloma	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	**Johnson & Johnson's Xarelto** (rivaroxaban) for acute coronary syndrome	PDUFA date
June 29	**Astellas Pharma's Betanis** (mirabegron) to treat overactive bladder	PDUFA date
	July 2012	
July 17	**Vivus' Qnexa** (phentermine + topiramate) for weight loss	PDUFA date (extended from April 17)
July 24	**GlaxoSmithKline's Tykerb** (lapatinib) **+ Roche's Herceptin** (trastuzumab), supplemental indication for HER2+ metastatic breast cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
July 25	Discussion of presurgical identification of clear-cell carcinoma of the kidney using an imaging test	FDA's Oncologic Drugs Advisory Committee (ODAC)
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 27	**Salix Pharmaceuticals and Progenics Pharmaceuticals' Relistor** (subcutaneous methylnaltrexone bromide) for chronic non-cancer pain	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)	PDUFA date
	August 2012	
August 4	**Regeneron Pharmaceuticals** and **Sanofi's Zaltrap** (aflibercept) for colon cancer	PDUFA date
August 12	**Talon Therapeutics' Marqibo** (vincristine sulfate liposomes injection) for Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL)	PDUFA date (extended from May 13)
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

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	Other 2012	
September 5	**Salix Pharmaceuticals' Provir** (crofelemer) for HIV-related diarrhea	PDUFA date (extended from June 5)
September 8	**Ironwood Pharmaceuticals and Forest Laboratories' linaclotide** for irritable bowel syndrome	PDUFA date
September 10	**Navidea Biopharmaceuticals' Lymphoseek**, a radioactive agent for tracing lymph nodes in cancer patients	PDUFA date (extended from June 10)
September 23	**Regeneron's Eylea** (aflibercept) for central retinal vein occlusion (CRVO)	PDUFA date
October 21	**Impax Laboratories' IPX-066** for Parkinson's disease	PDUFA date
October 29	**Cornerstone Therapeutics' CRTX-080** to treat hyponatremia	PDUFA date
	2013	
January 29	**Sanofi/Genzyme and Isis Pharmaceuticals' Kynamro** (mipromersen) for homozygous familiar hypercholesterolemia	PDUFA date