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

- **ADCOCK INGRAM's Doxyfene and Synap Forte (dextropropoxyphene)** – This South African pharma "insists" its painkiller is safe, and the company said it has studies to prove that, but South African authorities have moved to join regulators in the U.S. and Europe to ban sales. A South African court also barred sales pending a court appeal of South Africa's Medicines Control Council decision.
- **ALIMERA SCIENCES and PSIVIDA's Iluvien (fluocinolone acetonide)**, a drug-eluting implant for diabetic macular edema, was rejected yet again by the FDA, which asked the company to run two new clinical trials before approval. The company said the FDA found the clinical trials did not prove the implant is safe and effective and that the benefits did not outweigh the side effects, including cataracts and increased intraocular pressure.
- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran)** – The company admitted this anticoagulant to prevent strokes in atrial fibrillation patients has been linked to 260 deaths worldwide but said the rate is lower than predicted.
- **CHELSEA THERAPEUTICS' Northera (droxidopa)** was granted priority review by the FDA to treat symptomatic neurogenic orthostatic hypotension in patients with primary autonomic failure, such as Parkinson's disease. It already has orphan drug status. The PDUFA date is March 28, 2012.
- **COOPERVISION's Avaira** – The recall on these silicone hydrogel contact lenses was expanded to include some Avaira Sphere in addition to the Avaira Toric, all made in the U.K. The problem is the same: an excess of silicone oil residue, which can cause severe burning and discomfort.
- **COVIDIEN's Pennsaid (diclofenac sodium)** – At the FDA's request, Covidien suspended distribution of 15 mL sample bottles of Pennsaid, a topical painkiller for osteoarthritis of the knee. The FDA said it had received five reports of patients incorrectly using the medication, either taking it orally or in the eye.
- **DYAX's Kalbitor (ecallantide)** – The company is withdrawing the marketing authorization application first submitted to the European Medicines Agency (EMA) in June 2010 for this hereditary angioedema drug, saying it was unable to provide sufficient information to address the outstanding clinical issues identified during the evaluation of the application.
- **Electronic medical records (EMRs)** – According to a survey of 74 community hospitals (<300 beds) by **Anthelio Healthcare Solutions**, 23% have a fully functional EMR, 69% have begun implementation, and only 8% still haven't started EMR

implementation or don't plan to do so. In addition, 43% of hospitals responding to the survey are participating in a health information exchange (HIE), 28% would like to participate in an HIE, and 29% have no interest in an HIE.

- **ENDO PHARMACEUTICALS' octreotide** – The company said it has discontinued development of this growth hormone inhibitor designed to treat abnormal growth of hands and feet.

- **GE HEALTHCARE's Senographe Essential** – The company submitted the first module of a rolling submission for a premarket approval (PMA) application for this 3D breast tomosynthesis machine.

- **GERON** is halting development of its stem cell programs. This included stopping enrollment in the GRNOPC1 embryonic stem cell study in spinal cord injury patients, though existing patients will continue to be followed. Geron is looking for partners to take over the programs' assets and is laying off much of its staff.

- **LUPIN**, a generic drugmaker in India, is buying **I'rom Pharmaceutical**, a Japanese pharma that manufactures specialty injectable drugs.

- **MEDTRONIC's Physio-Control unit**, which makes heart monitors and external defibrillators, is being sold to **Bain Capital**.

- **MERCK's Janacti (sitagliptin + pioglitazone)** – MSD withdrew its European marketing authorization application for this fixed-dose combination drug for Type 2 diabetes, saying the decision was based on its review of the regulatory and commercial prospects.

- **NAPO PHARMACEUTICALS and SALIX PHARMACEUTICALS' crofelemer** – Napo canceled its deal with Salix, saying Salix failed to submit an FDA application for this therapy for HIV-related chronic diarrhea in a timely manner. Napo claimed Salix materially breached the collaboration agreement by unnecessarily stalling the advancement of the drug.

- **NEUROGESX's Qutenza (transdermal capsaicin)** – The FDA accepted the sNDA filing for a new indication of this drug – treatment of HIV-related neuropathic pain. Qutenza is approved already for postherpetic neuralgia.

- **NOVARTIS** developed a new class of experimental malaria drugs, its second in 14 months – imidazolopiperazines. According to a study published in the journal ***Science,*** this class attacks malaria-causing parasites earlier than currently approved therapies, making them useful both for treatment and prevention. Human clinical trials are expected to start in 2012.

- **NUPATHE's Zelrix (transdermal sumatriptan)** – After meeting with the FDA, company officials said they plan to resubmit the new drug application (NDA) for this migraine therapy. In August 2011, the FDA issued a complete response letter, which the company said raised questions about chemistry, manufacturing, and safety.

- **Obamacare** – The Supreme Court will review the constitutionality of the insurance mandate in the healthcare reform law, with oral arguments expected in March 2012 and a decision in June 2012. In addition, the court will review a provision of the law that extends Medicaid to cover a larger number of poor people, which 26 states have challenged as an unconstitutional coercion of state governments.

- **ORGANON's Remeron (mirtazapine)** – The results of a study funded by the National Institute on Drug Abuse (NIDA), published in the ***Archives of General Psychiatry***, found this antidepressant helps addicts overcome methamphetamine addiction. The 12-week, 60-patient study found patients receiving both counseling and Remeron were less likely to have a positive urine test for methamphetamine. However, several of the men gained "substantial" weight.

- **PFIZER's Prevnar 13** – The FDA's Vaccines and Related Biologics Advisory Committee voted 14-1 that this pneumonia vaccine is safe and effective for adults age ≥50. Prevnar 13 already is FDA approved to treat children age ≤5. Pfizer is currently conducting an 85,000-patient study in the Netherlands to assess Prevnar in adults, with results expected in 2013.

- **REGENERON's Eylea (aflibercept)** was approved by the FDA to treat wet AMD with either once a month or once every other month injections. It will compete with Roche/Genentech's Avastin (bevacizumab) and Lucentis (ranibizumab).

- **SALIX PHARMACEUTICALS' Xifaxan (rifaximin)** – The FDA's Gastrointestinal Drugs Advisory Committee gave the green light to the company's proposal for a clinical trial in irritable bowel syndrome with diarrhea (IBS-D) despite concerns about the trial design, the drug's efficacy, and the unknown mechanism of action.

- **SXC HEALTH SOLUTIONS** is buying **HealthTrans**, a privately held pharmacy benefits manager.

NEWS IN BRIEF

ARCA BIOPHARMA's Gencaro (bucindolol hydrochloride) – positive analysis

The company said an analysis of atrial fibrillation and pharmacogenetic data from the Phase III BEST heart failure trial showed a 41% risk reduction in new onset atrial fibrilla-tion with this beta blocker. The effect was even greater (74% risk reduction) in heart failure patients with a specific genotype (homozygous arginine at beta-1 389), which the company believes 50% of the U.S. population has. The FDA rejected Gencaro in 2009 but last year granted a special protocol assessment for another trial in certain heart failure patients.

INCYTE's Jakafi (ruxolitinib) – first JAK inhibitor approved

This twice-daily JAK1/2 inhibitor, a first-in-class orphan drug, was approved to treat myelofibrosis, and it was approved more than two weeks ahead of the PDUFA date. Richard Pazdur, MD, director of the FDA's Office of Hematology and Oncology Products in the Center for Drug Evaluation and Research (CDER), said, "Jakafi represents another example of an increasing trend in oncology where a detailed scientific understanding of the mechanisms of a disease allows a drug to be directed toward specific molecular pathways. The clinical trials leading to this approval focused on problems that patients with myelofibrosis commonly encounter, including enlarged spleens and pain."

NERVIANO MEDICAL SCIENCES' danusertib (PHA-739358) – may treat neuroendocrine prostate cancers

This aurora kinase (AURKA) inhibitor may be effective in neuroendocrine prostate cancers (a very lethal form of the disease) that overexpress the AURKA and MYCN genes. The drug failed in a general trial in prostate cancer, but Weill Cornell Medical College researchers believe that may be because its effect is specific to neuroendocrine tumors.

The researchers reported in ***Cancer Discovery***, a journal of the American Association for Cancer Research (AACR), on a study that found (1) AURKA and MYCN genes are overexpressed and amplified in 40% of neuroendocrine prostate cancers and (2) PHA-739358 inhibited the growth of these neuroendocrine tumors. The study was funded by the Prostate Cancer Foundation, the Ann and William Bresnan Foundation, the Early Detection Research Network, and the Department of Defense.

Oral contraceptives – indirectly causing prostate cancer?

Oral contraceptives are being blamed for an increase over the past 40 years in the incidence of prostate cancer in men. In an article published in the ***British Medical Journal***, researchers said the amount of estrogen entering the water supply may be at least partly responsible for the rise in prostate cancers. The investigators examined use of contraceptives and rates of prostate cancer in ~100 countries and found that where the use of oral contraceptives was high, so was the rate of prostate cancer. *Of course, this could be an association, not a causal relationship.*

RECKITT BENCKISER PHARMACEUTICALS' Suboxone (buprenorphine-naloxone) – longer is better, but how long?

A 653-patient, 12-week, outpatient study published in the ***Archives of General Psychiatry*** found this addiction treatment can help addicts decrease their dependency on prescription opioids, but significantly successful outcomes only occurred when treatment lasted 8-12 weeks, and the benefits disappeared when the drug was withdrawn.

Interestingly, counseling did not seem to matter; either the drug worked or it didn't whether or not the patient got counseling, which suggests Suboxone may be able to be prescribed in a primary care setting, not just at addiction or rehab centers.

In phase 1, patients got Suboxone for just 2 weeks, followed by a 2-week taper and then 8 weeks of follow-up ± counseling, and the success rate was only 6.6%. Patients who did not have successful outcomes at the end of phase 1 were invited to enter phase 2, which involved 12 weeks of the drug, a 4-week taper, and 8 more weeks of follow-up ± counseling. In this phase, the success rate was 49.2%, but by the end of the 8-week follow-up period, it dropped to 8.6%.

The obvious question is how long addicts need to take Suboxone. A 3.5-year follow-up of the patients in this study is under way and may answer that question.

ROCHE/GENENTECH's Avastin (bevacizumab) – no more on-label use in breast cancer

FDA Commissioner Margaret Hamburg, MD, announced that the FDA's final decision on this VEGF inhibitor in the treatment of metastatic breast cancer: withdrawal. Dr. Hamburg said there is no evidence it is safe and effective. However, Avastin will remain on the market in the U.S. because it is

indicated in several other cancers, so off-label use will be possible in breast cancer, and it continues to be approved for metastatic breast cancer in 80 other countries. But Roche isn't giving up; it plans to start a trial of Avastin + paclitaxel vs. paclitaxel alone in metastatic breast cancer.

SANOFI

- **Multaq (dronedarone) –** The French health system will stop covering this anticoagulant for non-permanent atrial fibrillation, beginning December 1, 2011.
- **SANOFI/GENZYME's Lemtrada (alemtuzumab) –** The company reported positive top-line results with Lemtrada in a second Phase III in relapsing-remitting multiple sclerosis vs. standard therapy with **EMD Serono/Pfizer's Rebif** (interferon beta-1a). In that 2-year, 840-patient trial, Lemtrada produced a 49% reduction in the annualized relapse rate and a 42% reduction in the worsening of disability.

Schizophrenia – underlying science clues

Two studies presented at the Society for Neuroscience meeting offered clues to the origin of and science behind this mental illness. The researchers pointed to prenatal infections as a risk factor, saying they may increase the risk of schizophrenia by reducing the number of NMDA receptors in the brain, and they found an enzyme targeting these receptors may account for the effects antipsychotics have on the disease.

A study by Canadian researchers found pregnant rats injected with a bacterial neurotoxin had fewer NMDA receptors in the brain and had impairments in learning and memory vs. controls (placebo). A Yale study found the striatal-enriched tyrosine phosphatase (STEP) enzyme is overexpressed in the brains of schizophrenics and reduces the number of NMDA receptors. This study also demonstrated that antipsychotics may help patients by indirectly reducing STEP levels, allowing NMDA receptors to rebound. This suggests STEP inhibitors may be a new approach to treating schizophrenia.

REGULATORY NEWS

FDA approvals/clearances

- **ABBOTT LABORATORIES' Abbott ESA Chagas [*Trypanosoma cruzi* (*E. coli*, Recombinant) Antigen]**, an *in vitro* enzyme strip assay for the qualitative detection of antibodies to *T. cruzi*. There are currently two donor screening tests to *T. cruzi*, but this is the first test licensed as a supplemental test.
- **EUSA PHARMA's Erwinaze (asparaginase *Erwinia chrysanthemi*)**, a TIW injection used to treat patients with acute lymphoblastic leukemia (ALL) who develop an allergy (hypersensitivity) to the *E. coli*-derived asparaginase and peg-aspargase chemotherapy drugs used to treat ALL. Erwinaze has orphan drug status.
- **INTELGENX TECHNOLOGIES' CPI-300 (high-dose bupropion hydrochloride) –** The company hopes to find a partner to commercialize this antidepressant by 2Q12.
- **MAQUET CARDIOVASCULAR's Cardiosave**, an intra-aortic balloon pump for treating patients with left ventricular failure, etc. The company plans to launch the pump in the U.S. in January 2012.
- **MEDTRONIC's AdaptiveStim with RestoreSensor**, a neurostimulation system for treating chronic back and leg pain with motion-sensor technology that adjusts the timing and level of stimulation according to patients' body movements.
- **POSITIVEID's iglucose system**, a technology that sends glucometer readings to an online portal, where individuals with diabetes can monitor their glucose levels and clinicians and family members can have access.
- **TANDEM DIABETES CARE's t:slim Insulin Delivery System**, which has a color touch screen, a rechargeable battery, and USB connectivity.
- **X-SPINE SYSTEMS' Calix PC Spinal Implant System**, which has a process to improve resistance to device expulsion.

FDA recalls

MIZUHO OSI's Modular Table Systems were recalled due to reports of patient falls.

European regulatory actions

- **AMGEN's Vectibix (panitumumab)** plus chemotherapy was approved to treat colorectal cancer in patients with a non-mutated, or wild-type, KRAS gene. Vectibix was originally approved as a stand-alone agent for patients with metastatic cancer who failed to benefit from chemotherapy.
- **Buflomedil-containing medications –** The EMA recommended all sales of these drugs for peripheral arterial occlusive disease (PAOD) be discontinued in all European Union member states because the adverse side effects outweigh the benefits of the medication.
- **MAQUET CARDIOVASCULAR's Cardiosave**, an intra-aortic balloon pump for treating patients with left ventricular failure, etc., received a CE Mark.

- **PFIZER's Vyndaqel (tafamidis)** was approved to treat a rare neurodegenerative disorder, transthyretin familial amyloid polyneuropathy. Pfizer said it plans to launch Vyndaqel in early 2012. In April 2011, the FDA rejected the application as incomplete.
- **STAAR SURGICAL's nanoFLEX Toric Collamer Single Piece IOL** was approved for treating astigmatism in cataract patients.
- The European Commission announced a comprehensive plan to combat **multidrug-resistant bacteria**. Using the public/private Innovative Medicines Initiative, the Commission hopes to accelerate development and approval of drugs to combat superbugs by (a) promoting "unprecedented" open sharing of preclinical knowledge among pharmas and drugmakers, (b) passing legislation to allow for more flexible and faster approval of novel antibiotics, and (c) to collaborate with governments for "adequate market and pricing conditions."

U.K.'s National Institute for Health and Clinical Excellence (NICE) actions

EISAI's Halaven (eribulin), a drug for advanced breast cancer, was rejected because of both side effects and cost.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	November 2011	
November 27	**Transcept Pharmaceuticals' Intermezzo** (zolpidem tartrate) for insomnia	PDUFA date
	December 2011	
December tba	**Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to be completed	Company announcement or medical conference presentation
December 1	Review of **risk evaluation and mitigation strategies** (REMS), including iPLEDGE for isotretinoin	FDA's Drug Safety and Risk Management Dermatologic and Ophthalmic Drugs Advisory Committees meeting jointly
December 5	Using scientific research data to support a **pediatric medical device claim**	FDA public workshop
December 7	**Pfizer's Inlyta** (axitinib) for advanced renal cell carcinoma and **Affymax's peginesatide injection** for anemia in chroic renal failure dialysis patients	FDA's Oncologic Drugs Advisory Committee (ODAC)
December 7	Expanding the indication for **Medtronic's CRT-D devices** to symptomatic NYHA Class II patients with LBBB, QRS ≥120 ms, and LVEF ≤30%	FDA's Circulatory System Devices Advisory Committee
December 8	**CardioMEMS' CardioMEMS HF Pressure Measurement System**, a permanently implantable pulmonary arterial pressure measurement system	FDA's Circulatory System Devices Advisory Committee
December 8	**Antares Pharma's Anturol** (transdermal oxybutynin ATD gel) for OAB	PDUFA date
December 8	**Bayer's Yaz, Yasmin, and Beyaz** (drospirenone) blood clot safety review	FDA's Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committees meeting jointly
December 9	**Johnson & Johnson/Janssen's Ortho Evra** (norelgestromin/ethinyl estradiol transdermal system) blood clot safety review	FDA's Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committees meeting jointly
December 12	**Alexza Pharmaceuticals' Adasuve** (loxapine inhalation powder) for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. Pulmonary safety is the key concern.	FDA's Psychopharmacologic Drugs Advisory Committee
December 13	**Endo Pharmaceuticals' Opana** (extended-release oxymorphone), a painkiller	PDUFA date
	January 2012	
January	**Pfizer's Prevnar 13** (PCV13), a pneumococcal vaccine for adults	PDUFA date
January 3	**Medical device labeling** feedback is sought	FDA deadline for public comment
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
	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 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 28	**Pfizer's axitinib** for advanced renal cell carcinoma	PDUFA date (*approximate*)
	March 2012	
March tba	**Anti-nerve growth factor (NGF)** drug class safety review	FDA's Arthritis Advisory Committee – originally scheduled for September 13, 2011, but postponed indefinitely, now March 2012
March 6	**Discovery Labs' Surfaxin** (lucinactant), a therapy 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,** a Hedgehog pathway inhibitor for advanced basal cell carcinoma in adults for whom surgery is not an option	PDUFA date
March 27	**Affymax and Takeda's peginesatide** for anemia	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 26	**Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in 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	
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