TRENDS-in-MEDICINE

October 30, 2011

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

- **ABBOTT** – The company reported two combinations of its hepatitis C drugs – ABT-450 (a protease inhibitor) + ritonavir + either ABT-333 (a polymerase inhibitor) or ABT-072 (another polymerase inhibitor) – looked good in Phase II studies in previously untreated patients and may cure hepatitis C (HCV) in as few as 12 weeks.

- **Alzheimer's disease** – The European Medicines Agency (EMA) issued a draft opinion that an MRI of hippocampal volume is a valid way for selecting people in the early, pre-dementia stages of Alzheimer's disease for clinical trials. The EMA is accepting public comment until November 1, 2011, and will then issue a final decision.

- **AMAG PHARMACEUTICALS** – AMAG's stockholders voted against the proposed merger with **Allos Therapeutics**, and the merger was terminated. Instead, AMAG plans a company restructuring to cut costs and realign the management team.

- **AREVA MED bought MACROCYLICS**, which produces chemical agents that allow antibodies or proteins to attach to radioactive isotopes for use in nuclear medical treatments of aggressive types of cancer.

- **ATRICURE's Synergy Ablation System** – The FDA's Circulatory System Devices Advisory Committee was divided on this surgical ablation for atrial fibrillation. The panel voted unanimously (9-0) that it is effective, but was split on safety (5-4 in favor, with 1 abstention). The panel also was split on approvability, voting 5-3 (again with 1 abstention) that the benefits outweigh the risks. *The FDA generally regards close votes as neutral, so it is difficult to predict what the final FDA decision may be.*

- **BAXTER INTERNATIONAL** said it settled issues raised in a January 2011 FDA warning letter about manufacturing issues and postmarket adverse event reporting at two plants in Puerto Rico. The company also said it resolved safety issues related to peritoneal dialysis solutions manufactured at its plant in Ireland.

- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran)** – The European label has been updated – and the company will advise European physicians – that renal function testing must be done before starting this anticoagulant.

- **BRISTOL-MYERS SQUIBB and ASTRAZENECA's dapagliflozin** – The FDA delayed the PDUFA date for this first-in-class SGLT2 inhibitor for Type 2 diabetes by three months (to January 28, 2012) in order to consider new Phase III data submitted by the companies.

- **CELL THERAPEUTICS' pixantrone** was resubmitted to the FDA for accelerated approval to treat patients with relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL) who failed ≥2 prior lines of therapy.

Trends-in-Medicine has no financial connections with any pharmaceutical or medical device company. The information and opinions expressed have been compiled or arrived at from sources believed to be reliable and in good faith, but no liability is assumed for information contained in this newsletter. Copyright ©2011. This document may not be reproduced without written permission of the publisher.

- **CIGNA** is buying another healthcare insurer, Tennessee-based **HealthSpring**, to boost its Medicare Advantage business. HealthSpring has 340,000 Medicare Advantage customers in 11 states, including Florida, New Jersey, Pennsylvania, and Texas, as well as a Medicare prescription drug business with more than 800,000 customers.

- **CUBIST PHARMACEUTICALS** is buying **Adolor**, which will give it ADL-5945, a treatment for chronic opioid-induced constipation that is in Phase II development.

- **DAVITA** – The Office of Inspector General (OIG) at the U.S. Department of Health and Human Services (HHS) reportedly is considering subpoenaing documents from DaVita related to Medicaid-covered infusion medications in New York.

- **EXELIXIS' cabozantinib** reportedly showed "profound" efficacy in the 315-patient EXAM trial in metastatic medullary thyroid cancer, nearly tripling survival from 4 months to 11.2 months. Exelixis hopes to do a rolling submission to the FDA.

- **FOREST LABORATORIES and IRONWOOD PHARMACEUTICALS' linaclotide** was accepted by the FDA for review as a treatment for irritable bowel syndrome with constipation (IBS-C). **Almirall** submitted the drug to European regulators in September.

- **GILEAD SCIENCES' Quad (tenofovir + emtricitabine + elvitegravir + cobicistat)** – This 4-drug cocktail was submitted to the FDA for approval to treat HIV.

- **KERYX BIOPHARMACEUTICALS' sulodexide** – An international trial failed to show any benefit of sulodexide vs. placebo in preventing kidney failure in patients with Type 2 diabetic neuropathy, causing the study to be halted with 1,248 patients enrolled. The results were published in the ***Journal of the American Society of Nephrology***.

- **MEDTRONIC's Phased RF Ablation System** – The FDA's Circulatory System Devices Advisory Committee rejected this RF ablation therapy for atrial fibrillation, voting 8-2 that the benefits do not outweigh the risks. The panel unanimously (10-0) agreed the device is effective, but they voted 9-1 that it isn't safe for patients with persistent AFib.

- **MERCK's Gardasil** – The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) approved recommendations calling for routine vaccination of boys aged 11 or 12 with three doses of HPV4 to protect against human papillomavirus (HPV).

- **Needleless injectors** – The FDA warned against using jet injectors to deliver the flu vaccine, saying there were no data to support their safety of effectiveness for flu vaccines. The warning caused some drugstore chains to stop giving flu shots altogether for now. The question many are asking is whether people who got a needleless flu shot need to get a repeat vaccination.

- **NOVARTIS subsidiary ALCON** – As part of its investigation of possible healthcare fraud, HHS subpoenaed Alcon records relating to payments to clinicians and relating to the marketing of several products, including **Vigamox** (moxifloxacin), an ophthalmic topical antibiotic.

- **PHARMAXIS' Bronchitol (inhaled mannitol)** – The Committee for Medicinal Products for Human Use (CHMP) recommended European approval as adjunctive therapy for adults with cystic fibrosis. CHMP initially gave Bronchitol a negative opinion based on pediatric trial data. Pharmaxis expects to launch the drug with Quintiles next year.

- **ROMARK LABORATORIES' nitazoxanide (NT-300)** – Flu symptoms lasted less than four days – a non-significant 109.1 hours with 300 mg BID (p=0.5208) but a significant 95.5 hours with 600 mg BID (p=0.0084) – with this antiviral drug vs. nearly five days (116.7 hours) for placebo patients in a Phase IIb/III trial. Nitazoxanide was originally developed to treat cryptosporidium in AIDS patients.

- **TRANS1** – The OIG subpoenaed records as part of an investigation of alleged false claims and Medicare fraud relating to this spine device company.

- **VERTEX PHARMACEUTICALS' Incivek (telaprevir)** – The company is launching a Phase IIIb trial to see if HCV patients can get away with just 12-24 weeks of treatment (+pegylated interferon and ribavirin) rather than the current 24-48 weeks (+pegylated interferon and ribavirin).

- **ZIMMER** got a 483 letter from the FDA citing at least 10 complaints about its manufacturing practices at one of its plants.

NEWS IN BRIEF

Annual chest x-rays – don't find or improve mortality in lung cancer

A 154,901-patient trial, published in the ***Journal of the American Medical Association***, found patients who received annual chest x-rays for 4 years were no less likely to die of lung cancer than patients who received usual care. The PLCO Cancer Screening Trial followed all these patients for 10 years, but there simply was no significant difference in the rate of lung cancer detection or lung cancer mortality between the two groups. The researchers concluded that the study provides

"convincing evidence that lung cancer screening with chest radiography is not effective."

BAYER's Yasmin or Yaz (progestin drospirenone) – more negative safety news

An FDA-sponsored retrospective review of the medical history of >800,000 women found these oral contraceptives as well as **Johnson & Johnson's Ortho Evra** (ethinyl estradiol + norelgestromin) patch and **Merck's NuvaRing** (ethinyl estradiol + etonogestrel) have a higher rate of venous thromboembolism (VTE) than older birth control drugs. The FDA is convening an advisory committee on December 8, 2011, to discuss the issue.

In addition, a Danish study published in the ***British Medical Journal*** reported on another study that found oral contraceptives with desogestrel, gestodene, and drospirenone were associated with at least the same risk of VTE as oral contraceptives with levonorgestrel.

GILEAD SCIENCES – partners with GlobeImmune

Gilead signed a worldwide license and collaboration agreement for the development and commercialization of GlobeImmune's therapeutic vaccine products for use in conjunction with Gilead's **Viread (tenofovir)** and other oral therapies for the treatment of chronic hepatitis B virus (HBV) infection. GlobeImmune will handle development of the HBV therapeutic vaccine through Phase Ia trials, after which Gilead may take over responsibility for clinical development. Gilead said the goal of the research collaboration is to create and develop therapeutic vaccine products that have specific HBV DNA antigens cloned into S. cerevisiae (a species of yeast). The companies expect the combination of a therapeutic vaccine with oral suppressive antiviral therapy could help increase surface antigen (HBsAg) loss with seroconversion.

LILLY

- **Effient (prasugrel)** – In a survey by CRTonline, 73% of cardiologists said the uptake of Effient has been slow because they are comfortable with **Sanofi's Plavix (clopidogrel)**, while 22% said it was due to fear of bleeding, 3% said the cost is prohibitive, and 3% said the black box and labeling are to blame.
- **Xigris (drotrecogin alfa)** – The FDA announced Lilly was pulling Xigris from the worldwide market after the PROWESS-SHOCK trial failed to show a survival benefit in patients with severe sepsis and septic shock. Xigris was approved 10 years ago.

Mammography – maybe screening doesn't improve survival

The vast majority of women whose cancer is detected through routine screening mammograms do not get a survival benefit from the early detection. That was the conclusion of an analysis by Dartmouth researchers published in the ***Archives of Internal Medicine***. The researchers found screening mammography may make no survival difference because the cancer might have been detected and successfully treated without such screening, the screening may lead to over-diagnosis, and treatment can lead to harm when it detects abnormalities that do not require intervention.

PFIZER

- **Chantix (varenicline)** – The FDA found Chantix did not increase hospitalizations for psychiatric problems like depression and suicidal thoughts in two federally-funded studies of more than 26,000 patients, though the Agency noted the findings are not "definitive." The FDA said, "New studies show that the benefits…still outweigh its risks…But the studies do not rule out an increased risk of other neuropsychiatric events."
- **Tygacil (tigecycline)** – Public Citizen petitioned the FDA to require a black box warning on the label of this antibiotic for complicated skin infections, intra-abdominal infections, and community-acquired pneumonia, saying it has a ~30% higher mortality rate than other widely-used antibiotics. The FDA issued a safety alert in 2010 and revised the label, but Public Citizen says the label warning is not sufficiently prominent. Public Citizen also wants the FDA to advise that Tygacil should only be used as a last resort.
- **Zyvox (linezolid)** – The FDA narrowed the serotonergic psychiatric treatments that interact with this antibiotic to serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs).

SANOFI

- **Apidra SoloStar pens** – The company reported a worldwide shortage of these delivery devices for short-acting insulin due to a manufacturing problem in its plant in Frankfurt, Germany. The company hopes to resume production in 1Q12. Availability of the pens in the U.S. may stop this month.
- ***Clostridium difficile* vaccine** – Two industry-funded studies presented at the Infectious Diseases Society of America meeting suggested this vaccine is promising to treat *C. diff*. The studies followed ~100 patients. The company reportedly plans to target high-risk patients.

REGULATORY NEWS

Congress questions Chinese heparin companies

Two Chinese companies linked to past shipments of contaminated ingredients in heparin are continuing to supply the U.S. market. At least that's what a congressional investigation found. Five Republican lawmakers, led by Rep. Fred Upton (R-MI), wrote to FDA Commissioner Margaret Hamburg, MD, asking why the FDA hasn't issued warning letters and/or import alerts to these firms even though the FDA issued warning letters and import alerts to other Chinese heparin firms. The legislators said they have "very serious public health concerns" arising from their investigation.

FDA strengthening generic guidelines

The FDA is writing new guidelines that will tighten the standards by which generic drugs, particularly drugs with a narrow therapeutic index, are compared to the brand (reference) drug. According to a story in the ***Wilmington (DE) News Journal***, Lawrence Yu, PhD, the FDA's deputy director for science and chemistry, said one of the new changes will be tighter standards for how fast active ingredients are absorbed in the bloodstream.

European regulatory actions

- **APNEX MEDICAL's HGNS System**, an implantable device for treating obstructive sleep apnea, was granted a CE Mark. The company plans a limited launch of the system in Europe in 2012.
- **BAXTER INTERNATIONAL's Preflucel influenza vaccine** – About 300,000 doses of this flu vaccine were recalled because the most recent batch has been causing side effects.

FDA approvals/clearances

- **ABBOTT's Vysis EGR1 FISH Probe Kit** was cleared as a diagnostic test to help separate acute myeloid leukemia (AML) patients into prognostic risk categories based on chromosomal status or changes.
- **ACCURAY's Dose Control System**, a radiation dose control system designed to work with the company's TomoTherapy System for breast cancer identification, received 510(k) clearance.
- **CANDELIS** received FDA 510(k) clearance for three cloud-based applications for accessing imaging data – Astra Plus (via a wide area network or WAN), Astra Lite (via a thin client), and Astra Mobile (via an Apple mobile product such as iPad or iPhone).
- **CATALENT PHARMA SOLUTIONS' Onfi tablets (clobazam)** was approved as a Schedule IV orphan drug for adjunctive treatment of seizures associated with a form of epilepsy, Lennox-Gastaut syndrome, in adults and children 2 years of age and older. The FDA also is requiring a Medication Guide be given to patients and caregivers.
- **Generic olanzapine** – Two companies – **Dr. Reddy** and **Teva** – have been given the green light to launch the first generics of **Lilly's Zyprexa**, an atypical antipsychotic to treat schizophrenia.
- **MASIMO's Radical-7** – This non-invasive pulse oximeter received both a CE Mark and FDA 510(k) clearance.
- **ROCHE/VENTANA MEDICAL SYSTEMS' Ventana Companion Algorithm HER2 image analysis technology** was cleared for use in combination with the company's iScan Coreo Au scanner and Virtuoso software to help pathologists diagnose breast cancer.
- **ST. JUDE MEDICAL's Ilumien**, which uses a combination of optical coherence tomography (OCT) and fractional flow reserve (FFR) to enhance the detection and treatment of coronary artery occlusion, was cleared for use.

FDA warning letters

ORAWELLUSA's HIV 1/2 Antibody Saliva Rapid Screen Test kits – The company stopped production of these test kits after receiving a warning letter from the FDA that it had not informed the FDA of its plan to commercialize the kits and had not secured an investigational device exemption (IDE) from premarket approval.

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 1	Discussion of development plans for **Adherex Technologies' sodium thiosulfate** injection, **Roche/Genentech's vismodegib**, **GlaxoSmithKline's pazopanib**, and **AstraZeneca/MedImmune's Medi-573**, and vote on **Gen-Probe's Progensa PCA3** prostate biopsy assay	Pediatric Oncology Subcommittee of the FDA's Oncologic Drugs Advisory Committee (ODAC)
November 2	Discussion of regulatory, academic, and industry perspectives on the development of **anticoagulant products in children**	Pediatric Oncology Subcommittee of the FDA's Oncologic Drugs Advisory Committee (ODAC)
November 2	**Merck's Vytorin** (ezetimibe/simvastatin) and **Zetia** (ezetimibe), supplemental NDA to reduce major cardiovascular events in patients with chronic kidney disease (CKD), based on the results of the SHARP trial	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
November 3	Clinical trial design issues related to antibacterials for **Community-Acquired Bacterial Pneumonia (CABP)**	FDA's Anti-Infective Drugs Advisory Committee
November 4	Proposed changes to the **Mammography Quality Standard Act (MQSA) policies and inspection procedures**, **review of soft copy mammography images, and breast density reporting**	FDA's National Mammography Quality Assurance Advisory Committee meeting
November 4	Clinical trial design issues related to antibacterials for **Hospital-Acquired Bacterial Pneumonia (HABP)**, including Ventilator-Associated Bacterial Pneumonia (VABP)	FDA's Anti-Infective Drugs Advisory Committee
November 5	**Johnson & Johnson's Xarelto** (rivaroxaban) for stroke prevention in AFib	PDUFA date
November 12	**Alimera Sciences' Iluvien** (sustained-release fluocinolone acetonide implant) for DME	PDUFA date
November 16	**Pneumococcal 13v vaccine** safety and immunogencity in adults >age 50	FDA's Vaccines and Related Biological Products Advisory Cmte
November 16	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for IBS-D	FDA's Gastrointestinal Drugs Advisory Committee
November 17	**5-HT4 agonists** for chronic idiopathic constipation-predominant irritable bowel syndrome (IBS-C)	FDA's Gastrointestinal Drugs Advisory Committee
November 17	**Organogenesis' Apligraf**, an oral therapy for treating surgically created gingival and alveolar mucosal surface defects in adults	FDA's Cellular, Tissue, and Gene Therapies Advisory Committee
November 18	**Regeneron's Eylea** (aflibercept, VEGF Trap-Eye) for wet AMD	PDUFA date
November 27	**Transcept Pharmaceuticals' Intermezzo** (zolpidem tartrate) for middle-of-the-night 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 Advisory Committee meeting jointly with the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee
December 1 Postponed	**Contura's Aquamid**, a polyacrylamide aesthetic dermal filler for moderate-to-severe facial wrinkles, nasolabial folds, etc.	FDA's General and Plastic Surgery Devices Advisory Committee
December 7	**Pfizer's Inlyta** (axitinib) for advanced renal cell carcinoma and **Affymax's peginesatide injection** for the treatment of anemia associated with chronic renal failure (CRF) in adult patients on dialysis	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 Advisory Committee meeting jointly with the FDA's Drug Safety and Risk Management Advisory Committee
December 9	**Johnson & Johnson/Janssen's Ortho Evra** (norelgestromin/ethinyl estradiol transdermal system) blood clot safety review	FDA's Reproductive Health Drugs Advisory Committee meeting jointly with the FDA's Drug Safety and Risk Management Advisory Committee
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
	Other 2011 events of interest	
4Q11	**Ophthotech's ARC-1905** primary endpoint results in Phase I trial in dry AMD	Company announcement or medical conference presentation

2012 FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
January	**Pfizer's Prevnar 13** (PCV13), a pneumococcal vaccine for adults	PDUFA date
January 28	**Bristol-Myers Squibb and AstraZeneca's dapagliflozin**, a first-in-class SGLT2 inhibitor for Type 2 diabetes	***New*** 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	**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 or bipolar I disorder	PDUFA date
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 6	**Discovery Labs' Surfaxin** (lucinactant), a therapy for infant respiratory disease	PDUFA date
March 27	**Affymax and Takeda's peginesatide** for anemia	PDUFA date
March 28	**Edwards Lifesciences' Sapien** transcatheter aortic valve	CMS expected to publish NCD decision memo
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
June	**Forest Laboratories and Ironwood Pharmaceuticals' linaclotide**, a treatment for IBS-C	PDUFA date
June 26	**Edwards Lifesciences' Sapien** transcatheter aortic valve	CMS final NCD expected