TRENDS-in-MEDICINE

November 13, 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
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SHORT TAKES

- **ASTRAZENECA's TC-5214 –** This antidepressant failed to do better than placebo in an 8-week, 295-patient trial in refractory depression.
- **BAXTER INTERNATIONAL's HyQ –** In a Phase III trial this IV investigational drug reduced the rate of severe bacterial infections. The company said patients might be able to give themselves a single infusion of HyQ every 3-4 weeks, rather than have to get it through an IV drip.
- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran) –** Health Canada warned that it has seen five cases of drug mix-ups due to confusion between Pradaxa and **Sanofi's Plavix** (clopidogrel) because of the similarity of their names.
- **Carisoprodol –** The U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) reported the number of emergency department visits due to misuse or abuse of this muscle relaxant, which is sold under several brand names including **Meda Pharmaceuticals' Soma**, more than doubled from 2004 to 2009 (from 15,830 to 31,763), and 77% of the cases involved ≥1 other prescription medication. The FDA recommended limiting carisoprodol use to 2-3 weeks.
- **CELGENE's Vidaza (azacitidine) plus SYNDAX PHARMACEUTICALS' entinostat –** Researchers at Johns Hopkins University found that combining these two agents improved survival in patients with recurrent metastatic non-small cell lung cancer by 2.4 months. The results were published in ***Cancer Discovery***.
- **CELLCEUTIX's Kevetrin –** The company asked the FDA for permission to conduct a Phase I trial of this chemotherapy agent in solid tumors.
- **EDWARDS LIFESCIENCES' Sapien XT –** The company was given a green light by the FDA to include lower-risk (operable) patients in PARTNER II, an ~2,000-patient Phase III study of this next-generation transcatheter aortic valve.
- **gp350 –** Researchers hope this Epstein-Barr virus (EBV) vaccine may prove able to prevent infectious mononucleosis and EBV-associated cancers, without necessarily preventing the EBV infection itself. Positive Phase III trials are being discussed.
- **Healthcare IT –** The Institute of Medicine (IOM) recom-mended that a new agency, not the FDA, be in charge of regulating healthcare information technology (IT). The IOM report warns FDA oversight might limit IT innovation and put patient safety at risk.
- **Hormone replacement therapy (HRT) –** A study published in the journal ***Menopause*** of >80,000 women in Southern California Kaiser Permanente HMO plans

found women who discontinued HRT had a 55% greater risk of hip fracture vs. women who stayed on HRT. The hip fracture risk increased as early as two years after stopping HRT and increased the longer the women were off HRT – even for women taking bisphosphonates.

- **JENNEREX BIOTHERAPEUTICS' JX-594** – A Phase II study presented at the American Association for the Study of Liver Diseases (AASLD) meeting found high doses of the genetically engineered vaccine extended survival of advanced liver cancer patients by almost 14 months, and low doses extended survival by 6.7 months.

- **K-V PHARMACEUTICAL's Makena (hydroxyprogesterone caproate, 17P)** – K-V is fighting back against cheaper compounded versions of this preterm labor drug. K-V complained to the FDA that some compounded versions of its drug do not have the appropriate active ingredient. The FDA is running its own tests of potency, safety, and purity to see if the quality charges are true.

- **LILLY and AMYLIN PHARMACEUTICALS' Byetta (exenatide BID) and Bydureon (weekly exenatide)** – The two companies have ended their strategic alliance on these Type 2 diabetes drugs, and Amylin is getting the rights back.

- **LILLY and BRISTOL-MYERS SQUIBB's Erbitux (cetuximab)** – The FDA expanded the approval for this EGFR inhibitor as add-on therapy to chemotherapy in advanced head and neck cancer. The drug was shown to extend survival in head and neck cancer patients 2.7 months longer than chemotherapy alone.

- **MERCK and ALK-ABELLO's Ragweed AIT**, a sublingual immunotherapy tablet, successfully relieved ragweed allergy, with transient local side effects, in two Phase III North American trials. The studies, which were presented at the American College of Allergy, Asthma, and Immunology meeting, found that giving the immunotherapy for four months before and during ragweed season reduced symptoms by a clinically significant 24% (low dose) to 27% (high dose) more than placebo.

- **NEUROSEARCH's pridopidine** – This experimental dopamine-modulating agent missed the primary endpoint in a Phase III study, published in ***Lancet Neurology***, in 437 patients with Huntington's disease. There was no significant improvement in the primary endpoint – change in the modified motor score (mMS) measuring 10 items relating to voluntary movements derived from the unified Huntington's disease rate scale (UHDRS). However, researchers were still optimistic about the drug.

- **OCTAPHARMA's Octagam (immunoglobulin)** – The FDA gave the company permission to resume distribution of Octagam. Last year, Octapharma voluntarily pulled certain batches off the market after thromboembolic events were reported.

- **OPEXA THERAPEUTICS' Tovaxin**, an anti-T-cell therapeutic vaccine in development for multiple sclerosis, was granted fast track status by the FDA.

- **PFIZER's ponezumab** – Pfizer stopped development of this passive immunotherapy targeting the C-terminal end of amyloid-β (Aβ) after considering data from ongoing studies in mild-to-moderate Alzheimer's disease.

- **ROCHE/GENENTECH and CURIS' vismodegib,** a Hedgehog pathway inhibitor for inoperable advanced basal cell carcinoma, was granted priority review by the FDA. The PDUFA date is March 8, 2012.

- **RXBIO Rx100** – The company won a contract from the U.S. Department of Health and Human Services' Biomedical Advanced Research and Development Authority to further develop its drug to protect against radiation exposure.

- **SALIX** is buying **Oceana Therapeutics** to get Oceana's **Solesta** (dextranomer microspheres, sodium hyaluronate), a bowel control drug.

- **TOCRIS BIOSCIENCE's fasudil** – A preclinical mouse study with this Rho-kinase (ROCK) inhibitor, which was published in ***Stroke***, suggested it may reduce lesion burden in patients with cerebral cavernous malformation (CCM). The researchers treated mice with 100 mg/kg/day from weaning to 5 months of age and found they had significantly fewer overall CCMs and fewer individual caverns vs. placebo.

- **TRIVASCULAR's Ovation** – The FDA approved a humanitarian device exemption (HDE) for this iliac/femoral stent graft for abdominal aneurysms.

NEWS IN BRIEF

ABBOTT

- **Kaletra (lopinavir + ritonavir).** Several public health groups around the world joined together to launch a global campaign to oppose Abbott's "monopoly" on this AIDS drug and to spur generic competition. The activists called Abbott's pricing for Kaletra "anti-competitive" and anti-innovation. In the U.S. they are asking the government to authorize generic competition under rules providing for the government use of patents. In Brazil and India lawyers will file formal challenges to Abbott's patent claims. In Colombia, the protest will take the form of a lawsuit for

a compulsory license authorizing generic competition. Other actions are planned in Peru, Thailand, Ecuador, Vietnam, Malaysia, China, and the Netherlands.

- **Trilipix (fenofibric acid).** The FDA sent an alert to primary care doctors, cardiologists, and pharmacists to advise them that, after reviewing the findings of the ACCORD trial, it found this cholesterol-lowering drug does not reduce the risk of heart attacks or strokes. The FDA also changed the label.

Adipotide – a weight loss drug that works *in animals*

In a preclinical study published in ***Science Translational Medicine***, daily injections of this investigational weight loss medication reportedly helped obese monkeys lose 11% of their body fat in just 28 days. The monkeys ate less, shed belly fat, and had positive changes in metabolic function and insulin resistance. The downside: dehydration, a "moderate" drop in phosphorus and potassium levels, and small kidney lesions in some animals, but no nausea or vomiting. The side effects went away after the drug was discontinued – but so did the weight loss. Monkeys that were not obese did not lose weight.

Exelixis' cabozantinib – positive data from 3 trials

At the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in San Francisco, Exelixis reported data from two ongoing trials that are investigating a lower starting dose of this tyrosine kinase Met and VEGFR2 inhibitor in cancer patients.

- **IST**, an investigator-sponsored, 23-patient, adaptive-design Phase I trial in metastatic castration-resistant prostate cancer (CRPC) patients. Preliminary data showed that a 40 mg daily starting dose resulted in high rates of bone scan response (a 61.5% decrease) as assessed by computer-aided detection (CAD). The 40 mg dose also had better tolerability than the 100 mg daily dose being used in a Phase II discontinuation trial. A second cohort of 11 patients was enrolled for a 20 mg daily dose. In the 9 evaluable 20 mg patients, six had stable disease on bone scans, and one had progressive disease. Based on these results, a third cohort of 13 patients at 40 mg/day will open soon.
- **Japanese study**, a 6-patient Phase I trial in advanced solid tumors. This also supports use of 40 mg/day. In the study, two patients with non-small cell lung cancer (NSCLC) had confirmed partial responses with target lesion shrinkage of 38% and 41%; three patients had stable disease, and one patient had progression.
- **Phase II extension study.** The company reported that pain intensity was significantly reduced with cabozantinib in the ongoing, non-randomized, single-arm expansion cohort of the Phase II discontinuation trial of 100 mg/day. Average worst pain improved in 28 of 29 patients. Median best pain reduction from baseline was 46%, and 59% of patients had ≥30% decrease in average worst pain. Pain improvement began by Week 3 in the majority of patients. In addition, narcotic use decreased with cabozantinib, with 56% decreasing their dose ≥30%. Pain relief was accompanied by improved sleep and reduced interference with activities of daily living.

Genetic testing for cancer – easier with new test

Researchers showed for the first time that it is possible to screen patients for a broad range of cancer-causing genetic mutations as part of normal clinical practice. In a study published in the journal ***Annals of Oncology***, researchers studied genetic screening of patients with NSCLC, but they said the approach can be used in a range of other cancers.

The researchers at Harvard Medical School and Massachusetts General Hospital Cancer Center developed a clinical test called SNaPshot that can test for more than 50 well-known mutation sites (hot-spots) in 14 key cancer genes (including EGFR, KRAS, BRAF, HER2, etc.). SNaPshot uses a technique called "multiplex PCR," which amplifies multiple mutation sites in different genes in a single polymerase chain reaction (PCR) experiment.

SNaPshot reportedly can be performed in most existing clinical molecular diagnostic laboratories affiliated with hospitals and other institutions, using equipment that is already available.

MERCK

- **DOJ investigation.** The U.S. Justice Department subpoenaed Merck, requesting information about the marketing and sales tactics for Integrilin (eptifibatide), a cardiac IIb/III inhibitor, as well as the antibiotic Avelox (moxifloxacin).
- **Nexplanon (etonogestrel).** This 3-year contraceptive implant was approved. It is inserted under the skin of a woman's upper arm with a minor surgical in-office procedure.
- **Rejections.** The FDA rejected two Merck drugs that are already approved in Europe, issuing complete response letters for:
  - **Nomac/E2** (Zoely in Europe), a birth control pill.
  - **tafluprost** (Saflutan in Europe), a prostaglandin analog for glaucoma.

NPS PHARMACEUTICALS' NPSP-558 – looking good in hypoparathyroidism

This experimental synthetic replacement for human parathyroid hormone showed promise in a Phase III trial. In an intent-to-treat analysis, 53% of patients treated with NPSP-558 achieved the primary endpoint (≥50% reduction in oral calcium and vitamin D supplements) vs. 2% of placebo patients. NPSP-558 already has orphan drug status for the treatment of hypoparathyroidism. NPS said it will submit NPSP-558 to the FDA next year.

Opioids – FDA clarifies REMS training portion

The FDA issued draft guidance on a training program for healthcare professionals who prescribe extended-release or long-acting opioids. The 2- to 3-hour continuing medical education (CME) would be required to have information on:

- How to recognize evidence of, and the potential for, opioid misuse, abuse, and addiction.
- Weighing the risk and benefits of opioid therapy.
- Appropriate patient selection.
- Managing, monitoring, and counseling patients on the safe use of these drugs.

The course is part of the FDA's new Risk Evaluation and Mitigation Strategy (REMS) for opioids. Prescribers aren't required to take the course, but drug manufacturers are required to fund courses, keep track of how many do take them, and report those numbers to the FDA. And the FDA said it may toughen the requirements if enough doctors don't get educated.

Osteonecrosis – not just a jaw or bisphosphonate problem

Glucocorticoids prescribed even for short periods to treat lupus, rheumatoid arthritis, etc., can be associated with osteonecrosis, according to data presented at the American College of Rheumatology meeting. Researchers investigated 172 osteonecrosis cases from between 1999 and 2006 and found 25% of the patients had been given at least one prescription for a glucocorticoid vs. only 5.2% of controls. In 92% of the cases, the osteonecrosis occurred in the hip, 2% were in the jaw, and 1.9% in the knee.

ROCHE/GENENTECH's Avastin (bevacizumab)

- **AMD.** The U.S. Department of Veterans Affairs (VA) reversed itself yet again. Retina surgeons at VA hospitals had been prescribing Avastin for wet age-related macular degeneration (AMD), but last month the VA ordered them to use **Lucentis** instead because of contamination concerns. Now, the VA has decided its doctors can prescribe Avastin for wet AMD after all – but only on a one-vial-per-patient basis. That will cost the VA more money (~$600 per injection) than compounded Avastin (~$50 per injection), but it is still far less than Lucentis (~$2,000). Patients also have to be fully informed of the potential risks.
- **Contamination.** The FDA found contamination problems related to the capping process and disintegrating gaskets at the California plant that makes this cancer drug.

THERION BIOLOGICS' PANVAC – promising cancer vaccine

Monthly injections of this cancer vaccine produced encouraging results in a small Phase I trial in 26 heavily pre-treated women with metastatic breast or ovarian cancer. The study, sponsored by the National Cancer Institute and published in ***Clinical Cancer Research***, reported that median survival in the 12 breast cancer patients was 13.7 months, with one woman still alive at 37 months. Among the 14 ovarian cancer patients, median survival was 15 months.

REGULATORY NEWS

FDA draft guidance for human medical device studies

The FDA issued draft guidance designed to encourage Phase I development of medical devices and stimulate innovation. The FDA is looking for just nine companies to pilot the new approaches in the guidance. The results of the pilots will help determine the final guidance. To qualify, a company should focus on innovative, early-stage development technologies that are most likely to benefit from the efficiencies of the program. Enrollment will begin on December 12, 2011, and continue for about 5 months or until a final guidance is published, whichever occurs first.

The FDA believes the new guidance documents will give companies and FDA device reviewers more flexibility to start investigational studies sooner while maintaining appropriate human subject protections. The new rules that clarify the IDE (Investigational Device Exemption) process include:

- **"Approval with conditions."** This is when the FDA allows patients to enroll in a study while issues – such as data analysis methods or study design assumptions – are being resolved.
- **"Staged approvals."** This is when the FDA allows studies to begin with a smaller group of subjects while companies gather additional data, prior to a larger general enrollment.

FDA extends 510(k) comment periods

- The FDA extended until November 28, 2011, the deadline for public comments on its draft guidance on when a new 510(k) notification application would be required.
- The FDA extended until January 3, 2012, the comment period on draft guidance for the approval path for automatic external defibrillators (AEDs).

FDA studying RFID technology uses

A 9-hospital FDA survey on use of radiofrequency identification (RFID) and real-time location systems found that 8 of the hospitals used the devices to keep track of patient monitors, infusion pumps, and other mobile hospital equipment rather than to fight internal theft.

Legislation to encourage generic drugs

Three bipartisan legislators – Rep. Charles Bass (R-NH), Rep. Jo Ann Emerson (R-MO), and Rep. Peter Welch (D-VT) – proposed the Federal Medical Assistance Percentage (FMAP) program, which would incentivize states to use lower-priced generic drugs in their Medicaid programs. Under the law, states that substitute more expensive brand-name drugs with generics would be allowed to keep half of the money they save.

Medicare approves cardiovascular *prevention* services

Starting next year, the Centers for Medicare and Medicaid Services (CMS) will pay for a number of preventive services designed to reduce cardiovascular disease. Under a new coverage decision, CMS will pay for one face-to-face visit each year to allow patients and their healthcare providers to determine the best way to help prevent cardiovascular disease. The visit must be furnished by primary care practitioners – a family practice physician, an internal medicine physician, or a nurse practitioner – in a doctor's office. During the visit, providers can, among other things, screen for hypertension and promote a healthy diet.

FDA approvals/clearances

- **CARESTREAM HEALTH's Vue Motion**, a medical image viewer that lets doctors view MRI scans and other imaging data via a website, an iPad, or another mobile device.
- **INFINITT's Xelis**, a cardiac tool which enables users to conduct left ventricle analysis and coronary CT angiography.
- **NEW YORK BLOOD CENTER's Hemacord**, the first licensed hematopoietic progenitor cells-cord (HPC-C) cell therapy for patients with disorders affecting the hematopoietic system (e.g., multiple myeloma, and cord blood transplants have been used to treat patients with certain blood cancers and some inherited metabolic and immune system disorders). The product was given a boxed warning about the risk of several possible fatal reactions – Graft Versus Host Disease (GVHD), engraftment syndrome, graft failure, and infusion reactions.

European regulatory actions

- **CLARET MEDICAL's Montage filtration system**, which is used to protect carotid arteries from brain embolism during vascular surgeries, was granted a CE Mark.
- **DUOCORT PHARMA's Plenadren**, a hydrocortisone replacement for adults with adrenal insufficiency, was approved. DuoCort is being purchased by **ViroPharma**.
- **MEDTRONIC's CoreValve** was granted a CE Mark for direct aortic (transaortic) implantation.

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

ASTRAZENECA's Faslodex (fulvestrant) – NICE rejected this aromatase inhibitor for postmenopausal women with metastatic breast cancer, saying there is no evidence it works better than existing therapies – **Novartis' Femara** (letrozole) or **Pfizer's Arimidex** (anastrozole) – in terms of overall patient survival.

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 16	**Pneumococcal 13v vaccine** safety and immunogenicity 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 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 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 Drugsand 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 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 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 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 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 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	**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