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

- **American College of Cardiology (ACC) –** In an online survey by Cardiovascular Research Technologies (***CRTonline.org***), 42% of cardiologists voted that the ACC is the professional society that best represents them, beating out the European Society of Cardiology (ESC) with 33%, the Society of Cardiac Angiography and Interventions (SCAI) with 21%, and the American Heart Association (AHA) with 4%.

- **AMGEN** is buying **Micromet**, which has several cancer drugs in development, including blinatumomab for acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL).

- **AVILA THERAPEUTICS and CLOVIS ONCOLOGY's CO-1686 –** The FDA approved an investigational new drug application (IND) for this targeted inhibitor of epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer (NSCLC), and a Phase I/II trial will start in the U.S. and Europe in 2Q12.

- **BIOMARIN PHARMACEUTICAL's BMN-111** has moved into Phase I clinical trial to treat achondroplasia, a genetic defect that causes abnormal cartilage and bone formation, leading to severely shortened bones. The drug would be injected daily from diagnosis through puberty.

- **CAPSTONE THERAPEUTICS' AZX-100 and TP-508 –** The company (formerly known as OrthoLogic) stopped development of both these compounds – AZX-100, which was in Phase II for dermal scarring, and Chrysalin (TP-508), a thrombin peptide for myocardial infarction prevention, which Capstone returned to the University of Texas Medical Branch at Galveston. The company is running out of cash and dealing with a qui tam (whistle-blower) lawsuit. It is still looking for a partner for AZX-100.

- **GUIDED THERAPEUTICS' LuViva Advanced Cervical Scan** was rejected by the FDA, but the company plans to seek an independent panel review of its premarket approval (PMA) application. LuViva also was submitted to European regulators.

- **GW PHARMACEUTICALS' Sativex (nabiximols) –** This oral cannabis-derived spray was submitted to the FDA as a treatment for severe pain associated with cancer.

- **INSMED's Arikace (liposomal amikacin) –** The FDA lifted the clinical hold on this inhaled drug for the treatment of non-tuberculous mycobacteria lung disease, and trials are expected to resume this year. However, the clinical hold in cystic fibrosis remains in place. In October 2011, the FDA said it wanted a 9-month toxicity test in dogs before lifting the cystic fibrosis hold.

- **OMNICARE –** The Federal Trade Commission (FTC) is suing to block Omnicare's acquisition of **PharMerica**, a competitor.

- ROCHE made a hostile bid to buy **Illumina**, saying the purchase is designed to strengthen its role in life science diagnostics. Roche intends to combine its existing Applied Science business with Illumina and move the business area's headquarters to San Diego CA.
- SANOFI/GENZYME's Fabrazyme (agalsidase beta) – Just days after the European Medicines Agency (EMA) said Genzyme may produce this Fabry disease treatment at the company's Framingham MA plant, the FDA followed suit and granted approval.

NEWS IN BRIEF

ALEXZA PHARMACEUTICALS' Adasuve (loxapine inhalation powder) – FDA decision delayed

The FDA delayed the PDUFA date to May 4, 2012 (from February 4, 2012) because it considered the company's updated risk evaluation and mitigation strategy (REMS) a major amendment.

Public Citizen's Health Research Group also wrote the FDA urging the Agency not to approve this inhaled antipsychotic for a new indication, treatment of acute agitation, charging that even a single dose can cause serious lung toxicity, which is especially concerning in patients with asthma and chronic obstructive pulmonary disease (COPD).

Anthrax vaccine – promising animal results

A study by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), published in the journal ***Vaccine***, found that monkeys vaccinated with an anthrax capsule vaccine were protected against lethal anthrax infection. This would be the first non-toxin anthrax vaccine effective in monkeys, and it is expected to work against possible vaccine-resistant strains of anthrax as well as in people whose immune systems may not respond to protective antigen alone, which is the basis of human vaccine for anthrax.

Gene therapy for blindness – moving closer to reality

University of Florida researchers have developed a gene therapy that they believe could correct retinitis pigmentosa, an X-linked genetic form of blindness caused by degeneration in photoreceptor cells. The research, which is still in the very early stage, was published in the ***Proceedings of the National Academy of Sciences***. In an NIH-funded animal study, the gene therapy cured animals, and the researchers now plan to repeat the studies on a larger scale with longer follow-up and to make a version of the carrier virus that will be safe for humans.

Interventional cardiology – is cath lab radiation causing brain cancer?

An article in ***EuroIntervention*** by Ariel Roguin, MD, PhD, and Jacob Goldstein, MD, both interventional cardiologists from Israel, cites four new cases of interventional cardiologists with brain tumors in the left hemisphere. In addition, they cited two additional cases in the literature plus three cases in interventional radiologists in the literature. The question is whether these brain tumors are the result of repeated low doses of ionizing radiation in the cath lab. Other cardiologists were asked to submit their own experiences.

MERCK's Vytorin (ezetimibe + simvastatin) – no new indication

The FDA rejected an expanded indication for this cholesterol-lowering medication but updated the label to include the SHARP trial findings that it effectively lowers LDL in chronic kidney disease (CKD) patients. As a combination product, FDA rules require showing that the combination is better than each component separately and that each component makes a contribution, but the SHARP trial did not study that. In November 2011, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 10-6 against recommending use of the drug in end-stage renal disease (ESRD) patients on dialysis but unanimously supported an indication in CKD.

NOVARTIS' Gilenya (fingolimod) – more safety issues

The EMA is reviewing the risk:benefit balance of this oral multiple sclerosis (MS) drug after reports of 11 patient deaths – 6 unexplained, 3 heart attacks, 1 heart rhythm abnormality, and the latest in the U.S. within 24 hours of the first dose. The review is expected to be completed in March 2012. The EMA's Committee for Medicinal Products for Human Use (CHMP) advised physicians to increase monitoring of patients after the first dose. The FDA also is investigating.

PFIZER

- **Bosutinib.** The FDA accepted the company's New Drug Application (NDA) for standard review of bosutinib to treat adults with previously treated Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML).
- **Revatio (sildenafil).** A preliminary study published in the ***New England Journal of Medicine*** suggested that this pulmonary hypertension drug may effectively treat children with a disfiguring growth disorder, severe lymphatic malformations.

Proton pump inhibitors (PPIs) – not a treatment for pediatric asthma

A 306-patient study published in the ***Journal of the American Medical Association*** found that acid suppression therapy – with **Takeda's Prevacid** (lansoprazole) in particular but by extension all PPIs – is not helpful in treating pediatric asthma and is associated with a 30% increase in respiratory infections and a signal for an excess in activity-related bone fractures.

Psilocybin – possible antidepressant

A study by U.K. researchers in 30 healthy volunteers, published in the ***Proceedings of the National Academy of Sciences***, found that IV administration of psilocybin – the active ingredient in "magic mushrooms" – is active in the part of the brain associated with depression. A second study by the same researchers, published in the ***British Journal of Psychiatry***, found that psilocybin enhanced volunteers' recollections of positive personal memories vs. placebo. The researchers suggested that psilocybin has potential as an antidepressant and are planning a small Phase I study.

RANBAXY – settled with Justice Department

To settle charges by the U.S. Department of Justice (DOJ) that it produced "adulterated, potentially unsafe" drugs that were illegal to sell in the U.S., Ranbaxy agreed to a consent decree filed by the DOJ. The agreement:

- Prevents the company from selling drugs made at four of its plants until those plants are in compliance with current good manufacturing practices (cGMP).
- Requires the company to remedy deviations from cGMP and correct data integrity problems.
- Calls for hiring a third-party expert to conduct audits of the facilities once they are in compliance to ensure that compliance is maintained.
- Strips the company of any 180-day marketing exclusivity arrangements for pending generic drug applications. However, generic atorvastatin apparently is not affected, and the facilities where it is produced remain approved to produce drugs for the U.S. market.

REGULATORY NEWS

CMS advisory panel can't decide how best to treat carotid artery disease

What's best for elderly Americans with carotid artery stenosis – medication, stents, or bypass surgery? The Centers for Medicare and Medicaid Services (CMS) recently convened a meeting of its Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) to consider this question, but the panel voted that there's not enough evidence to provide a clear answer on which is the best treatment. However, the panel was fairly confident that carotid endarterectomy is more beneficial than stents or medication alone for most patients with symptomatic carotid disease who are not considered high risk for adverse events from the surgery, voting that endarterectomy is the "favored" option.

MEDCAC chairman Clifford Goodman, PhD, senior vice president at **The Lewin Group**, said more data are needed, "The evidence base that could inform best clinical practice continues to evolve, and we're not done assembling the evidence on any of these alternatives."

CMS has not officially opened up a National Coverage Determination on the issue.

FDA draft guidance on pharma use of social media

The FDA issued draft guidance for pharmaceutical companies on how to interact with consumers on social media, but the guidance was criticized as not advising pharmas on their liability for information posted on their sites by third parties. One particular concern is how to handle information that could be considered an adverse drug reaction. The FDA is accepting public comments on the guidance through March 26.

FDA extends comment period on pediatric devices

The FDA is extending the comment period on pediatric medical devices to March 5, 2012, and the Agency will hold a public workshop February 15-16, 2012, to consider factors affecting the use of scientific research data to support pediatric medical device efficacy claims.

FDA orders generic *and* brand names used in ads

The FDA issued guidance that specifies that a drug's scientific name generally must be mentioned next to its brand name in promotional materials, including online ads. And the FDA wants the drug names to be prominent, not obscure.

FDA 2012 device priorities

The FDA's Center for Devices & Radiological Health (CDRH) said it will focus on several areas this year, including:

- Finalizing guidance documents related to boosting premarket programs.
- Making the recall process more efficient.

- Developing a postmarket surveillance strategy.
- Implementing a total product life cycle approach.
- Enhancing internal and external communication and transparency.
- Facilitating innovation.
- Strengthening its workforce.
- Issuing a proposal to clarify when the Agency can rely on clinical studies conducted in other countries.

FDA approvals/clearances

- **ALERE's nasal swab, office-based influenza A&B test** received a Clinical Laboratory Improvement Amendments (CLIA) waiver.
- **CAMBRIDGE TEMPERATURE CONCEPTS' DuoFertility Monitor** was cleared by the FDA as a temperature-taking tool to help predict ovulation for conception.
- **LEO PHARMA's Picato gel** was approved to treat actinic keratoses.
- **MEDTRONIC's Aquamantys SBS 5.0**, a sheathed bipolar sealer that uses saline and radiofrequency (RF) energy to enhance visualization and minimize blood loss during spine surgery, was given 510(k) clearance.
- **PFIZER's Inlyta (axitinib)** was approved to treat advanced renal cell carcinoma (RCC) patients who have not responded to prior therapy.
- **QUOTIENT BIODIAGNOSTICS' reagent red blood cell products** for use in blood typing, antibody testing, and antibody identification were cleared for use.
- **TAKEDA/MILLENNIUM's Velcade (bortezomib)** – The FDA approved a subcutaneous version of this multiple myeloma drug.
- **UCB's Keppra (levetiracetam)** was granted an expanded approval to treat epilepsy in children ages ≥1 month.

FDA recalls/warnings

- **ANGIODYNAMICS' NanoKnife** – The company initiated a voluntary U.S. recall of the Ablation Zone Estimator (AZE) software used by this device after the FDA said the AZE feature should undergo 510(k) review. The company stopped U.S. shipments of the NanoKnife system but plans to resume distribution without the AZE feature by May 2012.
- **CELGENE's Abraxane (nab-paclitaxel)** – The FDA issued a warning letter, saying the company's advertising at the American Society of Clinical Oncology (ASCO) 2010 misrepresented the data on this breast cancer drug.
- **CEPHALON's Treanda (bendamustine HCl)** – The company voluntarily recalled one lot of this drug for chronic lymphocytic leukemia (CLL) due to glass fragments found in a single vial.
- **DR. REDDY'S LABORATORIES' fondaparinux sodium** – The FDA warned the company that its promotional website does not prominently display a boxed warning about this injectable medicine for deep vein thrombosis (DVT) after surgery. The company redesigned the website, and the FDA closed the matter.
- **NOVARTIS' Gleevec (imatinib)** – The FDA issued a warning letter, saying the company's advertising cited one patient's successful use of this drug for chronic myelogenous leukemia (CML), implying that other patients could expect the same results.
- **ORIDION SYSTEMS** – The FDA narrowed the ban on distribution of this Israeli company's devices to just its infant neonatal intubated CO_2 sampling lines, allowing the firm to continue shipping most of its medical devices to the U.S. In December 2011, the FDA barred the U.S. importation of any Oridion device after the firm reportedly failed to resolve quality issues at its manufacturing plant in Israel.

European regulatory actions

- **FZIOMED's Dynavisc adhesion barrier gel** received a CE Mark for use in tendon and peripheral nerve surgery.
- **NOVARTIS' Signifor (pasireotide)** – CHMP recommended approval of this drug for Cushing's disease patients who cannot have surgery or for whom surgery hasn't been successful.

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

- **BRISTOL-MYERS SQUIBB and PFIZER's Eliquis (apixaban)**, a blood thinner, got a positive recommendation to prevent blood clots after hip or knee replacement surgery. NICE found it to be cost-effective.
- **TAKEDA's Daxas (roflumilast)** – a treatment for severe COPD. NICE said there wasn't sufficient evidence to justify adding it to triple therapy. NICE wants a trial of Daxas in combination with other commonly used treatments to prove the drug offers an advantage.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	January 2012	
January 30	Discussion of pediatric-focused drug safety reviews for **Novartis/Celgene's Focalin XR** (dexmethylphenidate), **Shire's Daytrana** (methylphenidate), **AstraZeneca's Seroquel** (quetiapine), **Johnson & Johnson's Pancreaze** (pancrelipase amylase), **Aptalis' Zenpep** (pancrelipase lipase), **Abbott's Creon** (pancrelipase protease), plus discussion of **Teva's Plan B One-Step**.	FDA's Pediatric Advisory Committee
January 31	Pediatric-focused safety reviews on vaccines, including **Pfizer's Prevnar 13** for pneumonia and **GlaxoSmithKline's Cervarix** for HPV	FDA's Pediatric Advisory Committee
	February 2012	
February 1	Reauthorization of **PDUFA-V**	Health subcommittee of House Energy and Commerce Committee hearing
February 7	FDA's proposed **user fees for biosimilars**	Health subcommittee of House Energy and Commerce Committee hearing
February 8	**Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in castration-resistant prostate cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
February 9	**Eisai's Dacogen** (decitabine) for treatment of acute myelogenous leukemia (AML) and **Cell Therapeutics' Pixuvri** (pixantrone dimaleate) for relapsed/refractory non-Hodgkin's lymphoma	FDA's Oncologic Drugs Advisory Committee
February 9	**NeurogesX's Qutenza** (transdermal capsaicin) for HIV-related neuropathic pain	FDA's Anesthetic and Analgesic Drugs Advisory Committee
February 10	Possible reclassification of **cranial electrotherapy stimulator (CES) devices** to Class III (requiring a PMA)	FDA's Neurological Devices Advisory Committee
February 15	Reauthorization of **FDA user fee program for medical devices**	Health subcommittee of House Energy and Commerce Committee hearing
February 17	**Corcept Therapeutics' Corlux** (mifepristone) for Cushing's syndrome	PDUFA date
February 22	**Vivus' Qnexa** (phentermine + topiramate), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
February 23	**Chelsea Therapeutics' Northera** (droxidopa) for symptomatic neurogenic orthostatic hypotension with primary autonomic failure	FDA's Cardiovascular and Renal Drugs Advisory Committee
February 23	**Forest Laboratories' Eklira** (aclidinium bromide) for chronic obstructive pulmonary disease (COPD)	FDA's Pulmonary-Allergy Drugs Advisory Committee
February 27	Review of evidence needed for approval of **anti-inflammatory ophthalmic drugs post-ocular surgery** and appropriateness of marketing a single bottle for use in both eyes post-surgery	FDA's Dermatologic and Ophthalmic Drugs Advisory Committee
February 28-29	Flu vaccine update, including **Pandemic Influenza Surveillance** and licensure pathways for pandemic flu vaccines	FDA's Vaccines and Related Biological Products Advisory Committee
	March 2012	
March 6	**Discovery Labs' Surfaxin** (lucinactant) for infant respiratory disease	PDUFA date
March 7	**NeurogesX's Qutenza** (transdermal capsaicin) for neuropathic pain	PDUFA date
March 8	**Roche/Genentech and Curis' vismodegib** for advanced basal cell carcinoma in adults for whom surgery is not an option	PDUFA date
March 12	Safety of **anti-nerve growth factor (anti-NGF) drugs** in development to treat a variety of pain conditions. The questions are: Do reports of joint destruction represent a safety signal, and does the risk:benefit balance favor continued development?	FDA's Arthritis Advisory Committee
March 26	**MAP Pharmaceuticals' Levadex** (dihydroergotamine inhalation) for migraine	PDUFA date
March 26-27-28	Oral arguments on the **legality of Obamacare**	U.S. Supreme Court
March 27	**Affymax and Takeda's peginesatide** for anemia	PDUFA date
March 28	**Bristol-Myers Squibb's Eliquis** (apixaban) to prevent strokes in AFib	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 18	**Vertex Pharmaceuticals' Kalydeco** (ivacaftor) for cystic fibrosis	PDUFA date
April 24	**Cell Therapeutics' pixantrone** for aggressive non-Hodgkin's lymphoma	PDUFA date
April 25	**Takeda's alogliptin**, a DPP-4 for Type 2 diabetes	PDUFA date
April 26	**Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in castration-resistant 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		
May 1	**Protalix Biotherapeutics' taliglucerase alfa**, an investigational Gaucher disease drug	PDUFA date
May 4	**Alexza Pharmaceuticals' Adasuve** (loxapine inhalation powder) for the acute treatment of agitation associated with schizophrenia/bipolar I disorder	***New*** PDUFA date
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
June 29	**Astellas Pharma's mirabegron** for treatment of overactive bladder	PDUFA date
July 26	**Amarin's AMR-101** (omega-3 fish oil EPA) to treat hypertriglyceridemia	PDUFA date
July 26	**Horizon Pharma's Lodotra** (low-dose prednisone) for rheumatoid arthritis	PDUFA date
July 27	**Onyx Pharmaceuticals' carfilzomib** for multiple myeloma	PDUFA date
July 30	**Regeneron's Arcalyst** (rilonacept) for gout	PDUFA date
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