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

NOTE: For full coverage of the American Association of Dermatology meeting, subscribe to *Trends-in-Medicine*.

SHORT TAKES

- **AMGEN** is buying **KAI Pharmaceuticals**, which is developing KAI-4169, an IV drug in Phase II development to treat hyperparathyroidism in chronic kidney disease patients undergoing dialysis.

- **EPICEPT's AmiKet (amitriptyline 4%, ketamine 2% cream)** was granted fast track status by the FDA to treat peripheral neuropathy induced by taxanes, which are chemotherapy drugs.

- **MERCK's Proscar and Propecia (finasteride) –** The FDA added a label warning that this drug for baldness and benign prostatic hyperplasia (BPH) can cause sexual dysfunction even after treatment is stopped.

- **Metformin –** A meta-analysis of 13 studies, published in ***PLoS Medicine***, questions the mortality value of metformin in Type 2 diabetes. The 9,560 patients given metformin had no difference in all-cause death or cardiac death vs. other treatment or placebo.

- **NOVARTIS' Gilenya (fingolimod) –** After reviewing adverse event reports for this oral multiple sclerosis medication, the Institute for Safe Medication Practices, a non-profit watchdog organization, recommended that the FDA substantially restrict use and beef up patient assessments, given the serious adverse events that have been reported.

- **NOVIAN HEALTH's Novilase Interstitial Laser Therapy (ILT) –** A multicenter premarket approval (PMA) trial has begun to expand use of this image-guided, minimally invasive therapy to include laser ablation of breast cancer tumors ≤2 cm in lieu of lumpectomy. The company plans to start a similar trial in Europe soon. Novilase ILT already has FDA 510(k) clearance for the treatment of breast fibroadenomas.

- **Oncology drugs –** In a survey published in ***Health Affairs***, ~50% of oncologists said, in general terms, that for a new cancer drug to justify its price, it should cost $50,000-$100,000 per life-year saved. However, when faced with the case of a hypothetical patient, the oncologists accepted much higher cost-effectiveness ratios, often several hundred thousand dollars per life-year gained.

- **QRXPHARMA's MoxDuo CR (morphine + oxycodone controlled-release) –** The company reported two small Phase I pharmacokinetic studies in healthy volunteers were successfully completed, with sustained blood levels for ≤24 hours. The studies suggested QD or BID dosing is possible and showed no interaction with food. The

company plans to start Phase II proof-of-concept studies in mid-2012. MoxDuo CR has an abuse deterrence formulation that limits crushing or dissolution in alcohol or water.

- **RECOR MEDICAL's Paradise** – The company released updated data from the first-in-man REDUCE trial of this ultrasound transcatheter renal denervation system for treating resistant hypertension, showing that systolic blood pressure was reduced by a statistically significant 36 mmHg in 8 patients at 90 days. Paradise already has a CE Mark.

- **ST. JUDE MEDICAL's Riata leads** – The company asked the journal ***HeartRhythm*** to retract a study by Robert Hauser, MD, an electrophysiologist at Minneapolis Heart Institute, that suggested these ICD leads are linked to at least 20 deaths, saying the study contains "inaccuracies and a biased comparison." However, the journal rejected the request, saying the article had been extensively peer-reviewed before publication.

- **SEATTLE GENETICS and TAKEDA/MILLENNIUM's Adcetris (brentuximab vedotin)** – Both companies plan to collaborate with **Roche/Ventana Medical Systems** to develop a diagnostic test to identify patients who would best respond to this drug, which is approved to treat relapsed/refractory Hodgkin's lymphoma and systemic anaplastic large cell lymphoma (ALCL). Three cases of progressive multifocal leukoencephalopathy (PML) have been reported in Adcetris patients, and finding a way to identify responders could help with risk:benefit decisions.

- **TAKEDA** is buying **URL Pharma**, which will give it **Colcrys** (colchicine), an FDA-approved treatment for gout flares.

- **U-SYSTEMS' somo-v Automated Breast Ultrasound System (ABUS)** – The FDA's Radiological Devices Advisory Committee voted 13-0 that expanding the use of this screening tool to dense breast tissue was safe and effective and that the benefits outweighed the risks in women with normal findings on mammography and no previous clinical breast surgeries or interventions.

- **VIROPHARMA's Vancocin (vancomycin)** – The FDA did not grant the company three-year market exclusivity for this antibiotic and, instead, approved three generic versions. The company plans to seek an injunction to prevent the launch of the generics, but that is probably a very long shot since the FDA issued a long and detailed explanation of its decision. And the Federal Trade Commission is looking into whether ViroPharma engaged in unfair trade practices with Vancocin.

- **VIVUS' Qnexa (phentermine + topiramate)** – The FDA extended the PDUFA date for this obesity drug by three months to July 17, 2012. The company said it submitted new materials on its risk evaluation and mitigation strategy (REMS) to the FDA on April 4, 2012. *The question is why the focus is on a REMS instead of getting a cardiovascular outcomes study under way.*

NEWS IN BRIEF

Autism – drug appears to reverse symptoms

A study published in the journal ***Neuron*** found that CTEP, an mGlu5 inhibitor, corrected many of the symptoms of autism – lack of sociability, physical awkwardness, hyperactivity – in a mouse model of the condition (Fragile X syndrome) by acting on the synapses between brain cells. Researchers were surprised that the drug worked on adolescent mice, suggesting that symptoms can be reversed even after the critical period of early brain development. *Several companies have CTEP inhibitors in development.*

BAYER's florbetaben – early Alzheimer's detection

The results of a Phase III trial to be presented at the American Academy of Neurology meeting indicated that this PET imaging agent is useful in helping to diagnose Alzheimer's disease earlier by detecting the beta-amyloid plaques in the brain that are hallmark signs of the disease. In the study, florbetaben PET scans were made of the brains of 200 people near death (some with suspected dementia and others without known dementia). The results were then compared to autopsy findings. The researchers found that florbetaben detects beta-amyloid with a sensitivity of 77% and a specificity of 94%.

Comparison of the visual assessment method proposed for florbetaben in clinical practice with the post-mortem diagnosis showed a sensitivity of 100% and a specificity of 92%. The lead researcher, Marwan Sabbagh, MD, a neurologist from Banner Sun Health Research Institute in Sun City AZ, said, "These results confirm that florbetaben is able to detect beta-amyloid plaques in the brain during life with great accuracy and is a suitable biomarker. This is an easy, non-invasive way to assist an Alzheimer's diagnosis at an early stage."

Federal healthcare transaction tax recommended – two state programs are potential models

A report by the Institute of Medicine (IOM) said the federal government should tax healthcare transactions to pay for a doubling in public health spending to $24 billion from the

current $11.6 billion. Minnesota and Vermont already have a healthcare transaction tax, and the federal tax could be modeled on those programs.

The IOM also said:

- The U.S. needs to add ~1.33 years to the life expectancy of 50-year-old women and 0.90 years to the life expectancy of 50-year-old men.
- The Department of Health and Human Services (HHS) should establish a specific per-capita health expenditure target to be achieved by 2030.
- HHS should develop a "robust research infrastructure" for establishing the effectiveness and value of public health and preventive strategies, mechanisms for implementation of those strategies, and comparative effectiveness.

Lenaldekar – potential new key to leukemia therapy

An article published in ***Blood***, the journal of the American Society of Hematology (ASH), described studies done with zebrafish to test Lenaldekar (LDK) as a potential new anti-leukemia agent. Researchers at the University of Utah screened 26,400 molecules and identified LDK as effective in eliminating immature zebrafish T cells and targeting human T-ALL cell lines without causing major toxicity to other cell types. After 14 days of treatment, >60% of zebrafish treated with LDK maintained long-term remission (>9 months) vs. 100% death with control by Day 40.

The zebrafish findings held up in mouse models of human T-ALL, with LDK significantly slowing disease progression without toxicity. Likewise, human cell line studies in other leukemias – chronic myeloid leukemia (CML) and B-cell ALL (B-ALL) – responded to LDK therapy.

LDK appears to work differently from current leukemia treatments, inhibiting both an important signaling pathway that promotes the survival of leukemia cells and a pathway that controls cell division. The researchers said they are working to discover LDK's cellular target, which they hope will ultimately help convert the compound into a drug that can be used in patients with leukemia.

Lung cancer – spiral CT screening cost-effective for some patients

Low-dose spiral CT screening for lung cancer may not be cost-effective for everyone, but a study published in ***Health Affairs*** found it is cost-effective for screening at-risk older smokers. An actuarial model analysis estimated that the cost per life-year to screen at-risk smokers was ~$19,000, which is comparable to the cost of colorectal cancer screening and less than breast cancer (~$31,000) and cervical cancer (~$50,000) screening, in part because fewer lung screenings involve a biopsy. The researchers also predicted that screening would lead to >130,000 additional lung cancer survivors in 2012.

Medical journal "balance" questioned – corruption claims deemed unfounded

A study published in ***Nature Biotechnology*** accused four major medical journals – ***The Lancet***, the ***New England Journal of Medicine***, the ***Journal of the American Medical Association***, and ***Lancet Neurology*** – of being "unbalanced" concerning physician-academic relationships with industry. The study – written by the co-founder of the Association of Clinical Researchers and Educators (ACRE) and colleagues – found little evidence that industry-physician relationships are harmful to patients. After reviewing >100 articles, the authors found the journals claimed that industry research and marketing are corrupt and, therefore, collaboration corrupts doctors, but the claims were not backed by evidence and balanced interpretation was frequently lacking.

Omega-3 fatty acids – don't prevent secondary CV events

A 14-study meta-analysis published in the ***Archives of Internal Medicine*** questioned the value of omega-3 fatty acids for secondary prevention in people with a history of cardiovascular disease (prior heart attack or stroke). The researchers pooled the data and found no differences in the risk of new cardiac events – sudden cardiac death, heart attack (fatal or non-fatal), cardiac-related chest pain, heart failure, or stroke – in people taking fish oil supplements vs. placebo.

This finding is far from the final word on the subject, however. The "jury is still out," said JoAnn Manson, MD, director of preventive medicine at Brigham and Women's Hospital in Boston.

In an accompanying editorial, two other experts said "the jury is still out" and suggested that there may be a role for omega-3 fatty acids in primary prevention. However, one of the authors said he recommends patients eat fish, not take supplements.

PFIZER's Mylotarg (gemtuzumab ozogamicin) – on the comeback trail?

An open-label, randomized, Phase III study published in ***The Lancet*** found that giving this orphan drug in fractionated doses reduced toxicity and increased event-free survival and overall survival vs. standard chemotherapy in previously untreated

acute myeloid leukemia (AML) patients ages 50-70. Mylotarg received accelerated approval in 2000 to treat AML, but the required postmarketing trial failed to show an improvement in survival, so the drug was taken off the market. *The question is whether the company will make an effort to bring it back.*

ROCHE/GENENTECH

- **Avastin (bevacizumab).** Two-year data from an 80-patient study in patients with diabetic macular edema (DME) found that Avastin was more effective in improving mean best-corrected visual acuity (BCVA) than laser photocoagulation. The results were published in the ***Archives of Ophthalmology***.
- **Rituxan (rituximab).** This monoclonal antibody failed to improve response rates in lupus nephritis patients in a 144-patient study published in the journal ***Arthritis & Rheumatism***. At one year, complete and partial responses combined was 56.9% with Rituxan vs. 45.8% with placebo (p=0.18). Partial response alone was 30.6% vs. 15.3%.

REGULATORY NEWS

FDA to start pilot program of ESRD technology

Of the 32 products submitted to the FDA for participation in the new Innovation Pathway, a new FDA program designed to help shorten the regulatory path for select medical devices, the Agency chose three devices for end-stage renal disease patients:

- An implantable **Renal Assist Device (iRAD)** being developed by the University of California, San Francisco.
- **Blood Purification Technologies' Wearable Artificial Kidney (WAK)**.
- **CreatiVasc Medical's Hemoaccess Valve System (HVS)**.

FDA to require device tracking capability

The FDA is expected to announce a stricter device monitoring program soon that incudes assigning a unique identifier number to each device to allow the FDA to better monitor malfunctions.

HHS delays ICD-10

The Department of Health and Human Services proposed a 1-year delay in its deadline for implementing the new ICD-10 diagnosis coding system until October 1, 2014, due to concerns about the difficulties with implementing a new standardized health claims form, known as Version 5010, for electronic health transactions. Providers need to implement Version 5010 before they can start using ICD-10. The proposed rule will be open for comments for 30 days.

FDA approvals/clearances

- **ANULEX TECHNOLOGIES' fiXate Tissue Band** received expanded clearance for use in binding intrathecal pain pump catheter devices.
- **ASTRAZENECA's Dutoprol** (metoprolol succinate ER/hydrochlorothiazide), a once-daily antihypertensive that combines a beta blocker and a diuretic, was approved.
- **INTRONIX TECHNOLOGIES' Myoguide**, an electromyographic-guided injection device used in managing pain and other applications, received FDA 510(k) clearance.
- **LILLY's Amyvid** (florbetapir) was approved for use in PET detection of amyloid proteins associated with Alzheimer's disease.
- **MEDTRONIC's CRT-D devices** were given an extended approval to treat less severe heart failure.
- **OSI SYSTEMS/SPACELABS HEALTHCARE's Arkon**, an anesthesia delivery system, was cleared.

FDA recalls/warnings

BAYER's Yaz and Yasmin (drospirenone + ethinyl estradiol) – After reviewing epidemiologic studies, the FDA took the advice of its advisory committee, which voted 21-5 to recommend the addition of a warning about a higher risk (up to 3-fold higher) for blood clots with oral contraceptives containing drospirenone than for pills with levonorgestrel or other progestins. Drospirenone is a synthetic version of progestin.

European regulatory actions

- **ABBOTT LABORATORIES' Humira** (adalimumab), a TNF inhibitor, was approved by the European Commission to treat moderate-to-severe ulcerative colitis.
- **ABIOMED's Impella cVAD**, a catheter-based heart pump, was approved for use during cardiac surgery or during or after percutaneous coronary intervention (PCI).
- **BAYER's Xarelto** (rivaroxaban) was submitted to European regulators for an additional indication to prevent pulmonary embolisms and deep vein thrombosis (DVT).

Regulatory news from other countries

Japan: **ABBOTT's Xience Prime** drug-eluting stent was approved.

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 18	Use of minimal residual disease as a biomarker for evaluating new drugs to treat **acute lymphoblastic leukemia (ALL)**	FDA public workshop in conjunction with the American Society of Clinical Oncology (ASCO)
April 25	**Takeda's alogliptin**, a DPP-4 for Type 2 diabetes	PDUFA date
April 25	**HeartWare's HVAD** left ventricular assist device	FDA's Circulatory System Devices Advisory Committee
April 26	**Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in castration-resistant prostate cancer	PDUFA date
April 26	**Boston Scientific/Cameron Health's S-ICD**, a lead-less implantable cardioverter defibrillator	FDA's Circulatory System Devices Advisory Committee
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
	May 2012	
May 1	**Protalix Biotherapeutics' Uplyso** (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	PDUFA date
May 6	**GlaxoSmithKline's Votrient** (pazopanib) to treat sarcoma	PDUFA date
May 8	**Regeneron Pharmaceuticals' Arcalyst** (rilonacept), an interleukin-1 inhibitor to prevent gout flares during initiaton of uric acid-lowering therapy	FDA's Arthritis Advisory Committee
May 9	**Pfizer's tofacitinib**, an oral JAK inhibitor, to treat rheumatoid arthritis	FDA's Arthritis Advisory Committee
May 10	**Gilead Sciences' Truvada** (emtricitabine + tenofovir) for HIV prevention	FDA's Antiviral Drugs Advisory Committee
May 10	**Arena Pharmaceuticals and Eisai's Lorqess** (lorcaserin) for obesity	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
May 10-11	**Trial design for obesity devices** (balloons, suture devices, bands, space-occupying devices, etc.), studies, and discussion of what is clinically meaningful weight loss	FDA's Gastroenterology and Urology Devices Advisory Committee
May 11	**Gilead Sciences' Quad** (emtricitabine + tenofovir + elvitegravir + cobicistat) for HIV	FDA's Antiviral Drugs Advisory Committee
May 13	**Talon Therapeutics' Marqibo** (vincristine sulfate liposomes injection) for Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL)	PDUFA date
May 15	**OraQuick's In-Home HIV test**	FDA's Blood Products Advisory Committee
May 16-17	**Natural history studies of rare diseases:** meeting the needs of drug development and research	FDA workshop
May 22	**Bristol-Myers Squibb's Eliquis** (apixaban), an anticoagulant for prevention of stroke in AFib ***– This is apparently not happening.***	***Not scheduled*** FDA's Cardiovascular and Renal Drugs Advisory Committee
May 23	**Johnson & Johnson's Xarelto** (rivaroxaban), an anticoagulant for a supplemental indication in acute coronary syndrome (ACS)	***Official*** FDA's Cardiovascular and Renal Drugs Advisory Committee
May 24	**St. Jude Medical's Amplatzer** and **Gore's Helex ASD Occluder** for atrial septal defect closure – discussion of current safety and effectiveness for these devices, first approved in 2001 and 2006, respectively	FDA's Circulatory System Devices Advisory Committee
May 24	**Pfizer/FoldRx Pharmaceuticals' Vyndaqel** (tafamidis meglumine) for the treatment of transthyretin (TTR) familial amyloid polyneuropathy	FDA's Peripheral and Central Nervous System Drugs Advisory Committee
May 30-31	Discussion of **analgesic treatment of chronic pain** – mechanisms, epidemiology, new data on opioid efficacy, etc.	FDA public workshop

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	June 2012	
June 5	**Salix Pharmaceuticals' crofelemer** for HIV-related diarrhea	PDUFA date
June 5	**Merck/Ariad Pharmaceuticals' Taltorvic** (ridaforolimus) for sarcoma	PDUFA date
June 8	**Forest Laboratories and Ironwood Pharmaceuticals' linaclotide** for IBS-C	PDUFA date
June 8	**Roche/Genentech's pertuzumab** in HER2+ advanced breast cancer	PDUFA date
June 13	**Edwards Lifesciences' Sapien** transcatheter aortic valve repair (TAVR), an expanded indication for high-risk, operable patients	FDA's Circulatory System Devices Advisory Committee
June 15	**Gilead Sciences' Truvada** (emtricitabine + tenofovir) for HIV prevention	PDUFA date
June 21	**Dune Medical Devices' MarginProbe System**, which uses electro-magnetic waves to characterize human tissue in real time and provides intraoperative information on a malignancy of the surface of an *ex vivo* lumpectomy specimen	FDA's General and Plastic Surgery Devices Advisory Committee
June 25	**QRxPharma's MoxDuo** (morphine + oxycodone) for pain	PDUFA date
June 26	**Edwards Lifesciences' Sapien** transcatheter aortic valve	CMS final NCD expected
June 27	**Arena Pharmaceuticals and Eisai's Lorqess** (lorcaserin) for obesity	PDUFA date
June 27-28	Risk:benefit of **metal-on-metal hip replacement** and **resurfacing**	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
June 28	**Bristol-Myers Squibb's Eliquis** (apixaban), an anticoagulant for the prevention of stroke in AFib	PDUFA date
June 29	**Astellas Pharma's mirabegron** for treatment of overactive bladder	PDUFA date
	Other 2012	
July 17	**Vivus' Qnexa** (phentermine + topiramate) for weight loss	***New*** 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
July 30	**Almirall and Forest Laboratories' aclidinium** inhaled therapy for chronic obstructive pulmonary disease (COPD)	PDUFA date
August 4	**Regeneron Pharmaceuticals** and **Sanofi's Zaltrap** (aflibercept) for colon cancer	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
September 10	**Navidea Biopharmaceuticals' Lymphoseek**, a radioactive agent for tracing lymph nodes in cancer patients	PDUFA date (extended from June 10)
October 21	**Impax Laboratories' IPX-066** for Parkinson's disease	PDUFA date
October 29	**Cornerstone Therapeutics' CRTX-800** to treat hyponatremia	PDUFA date