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…

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NOTE: Subscribe to ***Trends-in-Medicine*** for full coverage of the Association for Research in Vision and Ophthalmology (ARVO) meeting as well as in-depth coverage of three FDA panels: the FDA's Antiviral Drugs Advisory Committee on Gilead Sciences' Quad four-in-one pill for HIV, the FDA's Arthritis Advisory Committee on Pfizer's oral tofacitinib for rheumatoid arthritis, and the FDA's Endocrinologic and Metabolic Drugs Advisory Committee on Arena Pharmaceuticals' obesity drug Lorqess (lorcaserin).

SHORT TAKES

- **ABBOTT LABORATORIES** pleaded guilty to violating drug law and will pay $1.6 billion in civil and criminal misdemeanor fines to settle Department of Justice charges that it promoted anti-seizure drug **Depakote** (valproic acid) for unapproved uses in nursing homes.

- **ALLERGAN's Lap-Band –** The Office of the Inspector General (OIG) of the Department of Health and Human Services (HHS) subpoenaed Allergan over this gastric banding device for obesity. *A subpoena like this is often the first step in a Medicare False Claims investigation. Expect this investigation to take a long time and cost Allergan a bundle.*

- **ARENA PHARMACEUTICALS' Lorqess (lorcaserin) –** In its second attempt at getting approval for this obesity drug, Arena got the support of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee, which voted 18-4 in favor of approval, determining most of the safety issues have been resolved.

- **AREVA MED's lead-212 –** The company is collaborating on an unusual Phase I trial with the University of Alabama at Birmingham Hospital that will link lead-212, a radioactive element of medically pure radium-224 with **Roche/Genentech**'s **Herceptin (trastuzumab)** in a variety of solid tumors (pancreatic, ovarian, colon, gastric, endometrial, etc.).

- **FERRING PHARMACEUTICALS' Lysteda (tranexamic acid) –** A pooled analysis of two trials – presented at the American College of Obstetricians and Gynecologists – found that patients treated with 3.9 g/day of this non-hormonal medicine had significantly reduced blood loss among women with menorrhagia vs. placebo. Women age ≥45 had the largest decrease from baseline.

- **GTx's Capesaris (GTx-758) –** The FDA gave the company permission to begin a Phase II efficacy trial as second-line therapy for advanced prostate cancer that does not respond to hormone therapy. The trial will begin in 3Q12.

- **INSMED's Arikace (liposomal amikacin) –** The FDA lifted the clinical hold on this inhalable antibiotic for cystic fibrosis patients with pseudomonas lung infections after

the company revised the population in a trial. Discussion is ongoing between Insmed and the FDA about the protocol for the Phase III study.

- **REGENERON PHARMACEUTICALS' Arcalyst (rilonacept, IL-1 Trap)** – The FDA's Arthritis Advisory Committee voted unanimously (11-0) that this subcutaneously injected interleukin-1 inhibitor should not be approved to treat gout due to inadequate safety data. The panel voted 6-5 that Arcalyst is effective in treating gout flares when administered at 80 mg weekly for 16 weeks after a 160 mg loading dose, but the panel also voted 8-3 that the safety data are inadequate (particularly follow-up that was too short).

- **SEATTLE GENETICS and TAKEDA's Adcetris (brentuximab vedotin)** – The companies began a Phase III trial in CD30-expressing relapsed cutaneous T-cell lymphoma under a special protocol assessment (SPA) agreement with the FDA.

- **TALON THERAPEUTICS' Marqibo (vincristine sulfate liposomes injection)** – The FDA delayed its review of this drug for acute lymphoblastic leukemia (ALL) by three months, until August 12, 2012. In March 2012, the FDA's Oncologic Drugs Advisory Committee voted 7-4 (with 2 abstentions) that the benefits outweigh the risks.

NEWS IN BRIEF

AMGEN

- **Epogen (epoetin alfa) – bundling cutting use but increasing transfusions.** A study presented at the National Kidney Foundation meeting found the government change last year to a bundled payment system for dialysis has translated into the intended decrease in use of erythropoiesis-stimulating agents (ESAs) but also to a significant increase in transfusion rates. The study suggested that dialysis centers, driven by the revised incentives and new ESA usage guidelines, have yet to find the right medication level for some patients. Centers for Medicare & Medicaid Services (CMS) and FDA officials said they will review the findings to see if reimbursement policies or ESA guidance should be revised.

- **Prolia (denosumab) – cutaneous adverse events reported.** A review of FDA AERS database, presented in a poster at the Society for Investigative Dermatology meeting, found more than 40 serious cutaneous adverse events linked to this osteoporosis drug (given 60 mg every 6 months) over the 16 months after it was approved. These included angioedema, cellulitis, and pustular dermatitis, with nine patients requiring hospitalization. However, there were only a handful of serious adverse events reported with the oncology version (120 mg every 4 weeks). One would expect more serious adverse events with the higher dose, and the investigators had no explanation why the opposite was true.

Bisphosphonates – FDA warns against long-term use

An FDA analysis, published in the ***New England Journal of Medicine***, recommended doctors and patients be cautious about long-term use of these osteoporosis drugs, but the Agency did not specify exactly how long is too long, saying decisions should be individualized for each patient.

However, the FDA did say that women "at low risk for fracture or with a bone density near normal may be good candidates to stop therapy after three to five years, but older patients at higher fracture risk and bone density 'in the osteoporotic range' may benefit from continued therapy."

Breast brachytherapy – conflicting opinions, findings

- **Cianna Medical's SAVI – positive.** A 265-patient study presented at the American Society of Breast Surgeons meeting found that strut-based breast brachytherapy (SAVI) is an effective treatment for women with ductal carcinoma *in situ* (DCIS) of the breast, with low rates of recurrence and low toxicity. Breast brachytherapy reduces radiation therapy time from six weeks to just five days.

- **Complications – negative.** A study published in the ***Journal of the American Medical Association*** cautioned that breast brachytherapy had a higher rate of complications than whole breast radiation. However, the American Society of Breast Disease (ASBD) issued a statement calling the information in the article "misleading" and defending breast brachytherapy. ASBD said the study was not a clinical trial, small differences that were statistically significant may not be clinically significant, and doctors have learned more about how to do breast brachytherapy, so results have been improving.

Breast thermography – not ready to replace mammography

A 181-patient prospective study presented at the American Society of Breast Surgeons meeting found that near-infrared breast thermography – sometimes called a "no-touch breast scan" – identified only 50% of suspicious breast lesions that proved to be cancer on biopsy. Using a higher-sensitivity mode of breast thermography produced higher (87%) agreement with breast biopsy results, but specificity dropped

to <50%, and half of normal contralateral breasts were rated positive.

An investigator concluded, "No-touch breast scan cannot discriminate between benign and malignant lesions in patients with suspicious imaging abnormalities. The higher sensitivity mode results in an unacceptable number of false positives. I think we're still trying to determine the role of infrared thermography as a screening tool, and it certainly does not replace mammography as the gold standard for biopsy and for definitive diagnosis of breast cancer."

CELGENE's Revlimid (lenalidomide) – raises the risk of a second primary cancer

After a comprehensive review, the FDA issued a warning that this cancer drug raises the risk of developing a second primary cancer, particularly acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), and Hodgkin's lymphoma. The label was also updated. In a pooled analysis of three prospective, randomized Revlimid multiple myeloma trials, 7.9% of Revlimid patients vs. 2.8% of placebo patients developed a second primary malignancy ($p<0.001$) – "almost a three-fold increase."

GILEAD SCIENCES – FDA panel recommends 2 HIV drugs

- **Quad (elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate).** The FDA's Antiviral Drugs Advisory Committee voted 13-1 that this 4-in-1 pill is safe and effective for treatment-naïve adults with HIV. However, the panel also recommended monitoring patients quarterly for renal toxicity.

- **Truvada (tenofovir + emtricitabine).** The FDA's Antiviral Drugs Advisory Committee voted 19-3 to recommend approval of once-daily Truvada to prevent (lower the risk of contracting) HIV in at-risk people. The panel voted 19-3 that it should be approved for use by gay men and 19-2 (1 abstention) that it should be approved for use by discordant couples (heterosexual couples where only one is HIV-positive). The panel also voted 12-8 (2 abstentions) to allow use by others at risk for HIV through sexual activity. The questions the panel wrestled with included: Will patients be compliant? Will insurance cover the cost (~$11,000/year)? Will men see it as an excuse to stop using condoms? The PDUFA date is June 15, 2012.

Multiple sclerosis – FDA warning about controversial treatment

The FDA issued a warning about injuries and deaths associated with an experimental procedure for multiple sclerosis (MS) patients – dubbed "liberation therapy" – that treats chronic cerebrospinal venous insufficiency (CCSVI). Some researchers believe CCSVI, which is characterized by a narrowing (stenosis) of veins in the neck and chest, may cause MS or contribute to its progression, but the FDA noted that studies so far have been inconclusive, and the criteria for diagnosing CCSVI have not been adequately established.

Treating MS with balloon angioplasty or stents to widen narrowed veins in the chest and neck has been associated with death, stroke, detachment, and migration of the stents, damage to the treated vein, blood clots, cranial nerve damage, and abdominal bleeding. Use of devices for this purpose is not FDA approved, and the FDA warned investigators to follow FDA rules for clinical trials and get an investigational device exemption (IDE) first.

NOVARTIS' Signifor (pasireotide) – positive Phase III results in acromegaly

The results of the 358-patient Phase III PASPORT-ACROMEGALY trial – presented at a joint meeting of the International Congress of Endocrinology and the European Congress of Endocrinology – showed that this multigland somatostatin analog offered better disease control for patients with acromegaly than standard therapy.

At one year, significantly more patients getting intramuscular injections of 40 mg of long-acting pasireotide had full disease control vs. those getting injections of 20 mg long-acting Sandostatin (octreotide) – 31.3% vs. 19.2%, $p=0.007$. In addition, fewer patients needed their dose up-titrated with pasireotide (50.6% vs. 67.6%). Adverse events were fairly comparable between the two therapies, with a little less diarrhea, cholelithiasis, and headache with pasireotide.

Opioid investigation broadens – first casualty

The American Pain Foundation decided to disband after the Senate Finance Committee began an inquiry into its relationship with opioid manufacturers, particularly **Purdue Pharma** and **Johnson & Johnson/Endo Pharmaceuticals**. And the Senate panel expanded its investigation – which was based on ***MedPage Today/Milwaukee Journal Sentinel*** articles – to 10 professional organizations and pharmaceutical companies, seeking to clarify their financial connections with opioid manufacturers and the promotion of opioids for chronic pain.

PFIZER

- **Lyrica (pregabalin).** Lyrica failed to control painful diabetic neuropathy in one study, and the company halted a second trial in nerve-damaged HIV patients after an interim analysis showed no difference between Lyrica and placebo.
- **Tofacitinib.** The FDA's Arthritis Advisory Committee voted 8-2 to recommend approval of this JAK2 inhibitor for rheumatoid arthritis. The panel also voted unanimously (10-0) that it is effective overall and 7-2 (1 abstention) that it is safe. However, it also voted 2-8 that there isn't convincing evidence of radiographic efficacy.

ROCHE's dalcetrapib – abandoned for lack of efficacy

The data safety monitoring board (DSMB) for the Phase III dal-OUTCOMES trial recommended stopping the trial for futility, not toxicity. The DSMB found a lack of clinically meaningful efficacy for this cholesteryl ester transfer protein (CETP) inhibitor in the trial, which was evaluating the efficacy and safety of dalcetrapib when added to existing standard of care in patients with stable coronary heart disease (CHD) following an acute coronary syndrome (ACS). No safety signals were reported from the DSMB.

Roche has now terminated the dal-OUTCOMES trial, the other five studies in the dal-HEART program, and dalcetrapib development. *What does this mean for other CETP inhibitors?* Currently, there is no proof that raising HDL is beneficial, even though low HDL is a known cardiac risk factor. A positive dal-OUTCOMES trial would have helped the entire class, and its failure is likely to delay if not kill other CETP programs.

ST. JUDE MEDICAL
– Riata still a growing problem; Durata uncertain

Speakers at a session of the Heart Rhythm Society meeting focused on the safety of these implantable cardioverter defibrillator (ICD) leads suggested:

- The survival curve for Riata ST is worse than for Riata in the updated Veterans Affairs database.
- There are still mixed opinions about the safety of the newer Durata leads. The Durata construction is substantially different from Riata, and there have been no reports of externalized conducts with Optim-coated leads, but there were still concerns about long-term durability and internal lead lumens.

Type 1 diabetes – new hope for a cure

Researchers at the University of Florida and City of Hope National Medical Center in Duarte CA have devised a new combination therapy that reverses established Type 1 diabetes in mice. The findings, which were published in the journal ***Science Translational Medicine***, suggest a cure for human Type 1 diabetes may be possible. The two-step regimen involves bone marrow transplantation combined with growth factors to boost production of insulin-producing beta cells in the pancreas.

The researchers demonstrated that beta cells can come from other types of cells. The findings suggest that, given the right stimulation, patients with diabetes could produce the needed beta cells on their own instead of having to wait for transplants from donors. The double approach reversed late-stage diabetes in 60% of the mice in the study.

The researchers are working to form a national collaboration to further investigate and develop the new combination therapy. But it is still going to take a long time to become a reality – if it does at all.

VERTEX's VX-809
– missed primary endpoint, but still very encouraging

In a preplanned interim analysis of an ongoing Phase II study in 48 adult cystic fibrosis patients with two copies of the F508del gene mutation, the combination of VX-809 and Vertex's **Kalydeco** (ivacaftor) missed the primary endpoint. The combination significantly reduced sweat chloride levels from baseline to Day 28 but not between Days 28 and 56.

However, the combination significantly ($p=0.002$) improved breathing (FEV_1), with 46% having improvement of ≥5% and 30% having improvement of ≥10% at 56 days vs. 0 with placebo, which overshadowed the missed primary end-point.

In the study, patients got only VX-809 for the first 28 days, and then Kalydeco was added. So, the question is whether Kalydeco helps at all. Or could it even be a negative? *Perhaps the answer will be in the final details.*

Vertex did not provide details on the three doses tested or the mean absolute improvement in lung function for the combination patients. However, ***TheStreet.com*** reported that a company official said patients in all three dose groups responded to the therapy and that overall lung function was not driven by a relatively small number of "super responders."

Kalydeco is approved for a small subset (~4%) of CF patients with the G551D mutation of the CFTR gene. The combination

was tested in a broader population of CF patients. Complete data from this trial are expected in mid-2012. The company plans to start a pivotal Phase III trial after its end-of-Phase II meeting with the FDA. The therapy won't be cheap. Kalydeco alone costs ~$294,000 a year.

REGULATORY NEWS

FDA office in China – explorers?

In an FDA blog, the FDA official in charge of the Agency's China Office (Christopher Hickey, PhD) compared his job to Lewis & Clark's exploration of the Louisiana Territory, calling it a "fascinating, unpredictable, 21st century expedition to explore new public health frontiers." He referred to his staff as "frontiersmen" and a modern "Corps of Discovery," equating the Chinese nationals helping his staff with Sacagawea.

Among the challenges the FDA China Office faces are:

- Navigating a regulatory system that assigns responsibility to government agencies not by product category but by where the product is produced and distributed.
- Engaging Chinese regulators whose primary mission is export promotion.
- Dealing with the legacy of state-owned enterprises.

HHS announces innovation awards

HHS Secretary Kathleen Sebelius announced the first $122.6 million in awards for healthcare innovation, supporting 26 projects nationwide that are expected to save $254 million over three years, deliver high-quality medical care, and enhance the healthcare workforce. The projects, to be administered by CMS, include collaborations of leading hospitals, healthcare professionals, community organizations, and patient advocacy groups in urban and rural areas to address healthcare issues in local communities. Among the projects are:

- A telemedicine project in **Georgia**, linking Emory University with critical care units in rural parts of the state, aimed at reducing the need to transfer patients from rural hospitals to critical care units in Atlanta.
- A **Minnesota** program to create a patient-centered medical home for adults with disabilities and complex medical conditions – high-cost Medicaid patients – called Camp Courage.
- An **Ohio** initiative to extend the expertise of a children's hospital to local pediatric practices that treat children with complex chronic conditions and behavioral health problems with physician extension teams and telehealth.

FDA approvals/clearances

- BOSTON SCIENTIFIC received clearance for its **Advantio** pacemaker, **Ingenio** pacemaker (which the company plans to launch immediately), and its **Invive** cardiac resynchronization therapy (CRT) pacemaker.
- **CLINIGEN's Foscavir (foscarnet sodium injection)**, which will be marketed in the U.S. by **Hospira**, was approved for the treatment of HIV/AIDS-related cytomegalovirus (CMV) infections and herpes.
- **GEN-PROBE's Panther molecular diagnostics platform** was granted 510(k) clearance. Initially, it will be used in conjunction with the Aptima Combo 2 assay to diagnose *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, but it might eventually be used with other Aptima assays for women's health.
- **HITACHI's Echelon Oval**, a 1.5-tesla MRI scanner, was cleared.
- **MEDINOL's PioNIR Plus**, a bare-metal coronary stent marketed by **Johnson & Johnson** outside the U.S., was approved by the FDA.
- **ST. JUDE MEDICAL:**
  - **Assura** suite of CRT-D devices and ICDs. **Unify Assura CRT-D, Quadra Assura CRT-D,** and **Fortify Assura ICD** all were cleared for use.
  - **Ellipse ICD**, reportedly the smallest high-voltage ICD, was cleared.
- **SORIN GROUP's Tilda pacing leads, Vigila defibrillation leads,** and **Celerity left ventricular leads** were all approved.

European regulatory actions

- **CARDIO3 BIOSCIENCES' C-Cath Injection Catheter** received a CE Mark.
- **CELL THERAPEUTICS' Pixvuri (pixantrone)** was granted conditional authorization to be marketed as a treatment for non-Hodgkin's B-cell lymphomas.
- **LOMA VISTA MEDICAL's True Dilatation balloon valvuloplasty catheter**, which is designed to prevent balloon ruptures in balloon valvuloplasty and transcatheter aortic valve replacement (TAVR) procedures, received a CE Mark and will be launched at EuroPCR later this month.
- **VESSIX VASCULAR's V2 renal denervation system**, which uses a percutaneous radiofrequency balloon catheter, received a CE Mark to treat patients with uncontrolled hypertension despite taking at least three antihypertensive medications.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	May 2012	
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 23	**Johnson & Johnson's Xarelto** (rivaroxaban), an anticoagulant for a supplemental indication in acute coronary syndrome (ACS)	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
	June 2012	
June 5	**Merck/Ariad Pharmaceuticals' Taltorvic** (ridaforolimus) for sarcoma	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 20	**Onyx Pharmaceuticals' carfilzomib**, a treatment for relapsed and refractory multiple myeloma	FDA's Oncologic Drugs Advisory Committee (ODAC)
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 21	**Repligen's RG-1068**, an imaging agent to help identify abnormalities in pancreatic ducts	PDUFA date
June 25	**QRxPharma's MoxDuo** (morphine + oxycodone) for pain	PDUFA date
June 27	**Arena Pharmaceuticals and Eisai's Lorqess** (lorcaserin) for obesity	PDUFA date
June 27	**Onyx Pharmaceuticals' carfilzomib**, a treatment for relapsed and refractory multiple myeloma	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
	July 2012	
July 17	**Vivus' Qnexa** (phentermine + topiramate) for weight loss	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 27	**Salix Pharmaceuticals and Progenics Pharmaceuticals' Relistor** (subcutaneous methylnaltrexone bromide) for chronic pain not caused by cancer	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 2012	
August 4	**Regeneron Pharmaceuticals** and **Sanofi's Zaltrap** (aflibercept) for colon cancer	PDUFA date
August 12	**Talon Therapeutics' Marqibo** (vincristine sulfate liposomes injection) for Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL)	***New*** PDUFA date (extended from May 13)
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

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	Other 2012	
September 5	**Salix Pharmaceuticals' Provir** (crofelemer) for HIV-related diarrhea	PDUFA date (extended from June 5)
September 8	**Ironwood Pharmaceuticals and Forest Laboratories' linaclotide** for irritable bowel syndrome	PDUFA date
September 10	**Navidea Biopharmaceuticals' Lymphoseek**, a radioactive agent for tracing lymph nodes in cancer patients	PDUFA date (extended from June 10)
September 23	**Regeneron's Eylea** (aflibercept) for central retinal vein occlusion (CRVO)	PDUFA date
October 21	**Impax Laboratories' IPX-066** for Parkinson's disease	PDUFA date
October 29	**Cornerstone Therapeutics' CRTX-080** to treat hyponatremia	PDUFA date