TRENDS-in-MEDICINE

**April 8, 2012**

***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:** For full coverage of the American Association for Cancer Research meeting, subscribe to ***Trends-in-Medicine***.

## SHORT TAKES

- **ACCESS SCIENTIFIC's Powerwand** – A 157-patient study published in the ***Journal of the Association for Vascular Access (JAVA)*** found that this peripheral IV (PIV) catheter is an effective alternative to central lines and standard PIV catheters. They found it was successfully placed the first time in 95% of cases, with an IV therapy completion rate of 89%. Complication rates were low, and patient satisfaction was high.

- **ACTELION PHARMACEUTICALS** said it is redirecting its development efforts in the anti-inflammatory area to focus on a follow-up CRTH2 antagonist currently in Phase I clinical development after its lead CRTH antagonist, setipiprant, failed in both a Phase IIb study in asthma and a Phase III study in seasonal allergic rhinitis. Development of setipiprant is being discontinued, but the company claims the follow-on compound is more potent.

- **AMGEN** and **AstraZeneca** signed a deal to co-develop and commercialize five of Amgen's antibodies for potential use in the treatment of inflammatory diseases – psoriasis, asthma, ulcerative colitis, Crohn's disease, lupus, etc.

- **AMYLIN PHARMACEUTICALS' metreleptin** was submitted to the FDA to treat diabetes and/or hypertriglyceridemia in patients with lipodystrophy.

- **BAYER's regorafenib** – The company announced that preliminary results from a second Phase III trial, GRID, indicate this multikinase inhibitor met the primary endpoint, showing statistically significant improvement in progression-free survival in patients with gastrointestinal stromal tumors. Bayer plans to submit the drug for approval based on these results. *Remember: The overall survival improvement in the first Phase III gastric cancer trial was a statistically significant 1.4 months.*

- **BIOGEN IDEC's dexpramipexole** – The company has started enrollment in a 804-patient, 18-month, Phase III trial, EMPOWER, in amyotrophic lateral sclerosis (ALS) of this mitochondrial modulator, which was licensed from **Knopp Biosciences**.

- **BIOMET** is seeking to buy the worldwide trauma business of **Johnson & Johnson/ DePuy Orthopaedics**. J&J needs to divest this business to satisfy regulatory concerns over its purchase of **Synthes** in 2011.

- **COVIDIEN** is buying **Oridion Systems**, an Israeli company that makes respiratory devices.

- **EXPRESS SCRIPTS and MEDCO HEALTH SOLUTIONS** – The Federal Trade Commission has given its okay for these two companies to merge, though the decision was not unanimous. The new name will be **Express Scripts Holding Co.**

- **HIV** – A study published in the journal ***AIDS*** found that men who have sex with men while on HAART therapy may still be at risk for spreading the infection on to their partners. Even potent antiviral therapy does not completely suppress the virus in semen.

- **HPV vaccine** – A study published in the ***British Medical Journal (BMJ)*** suggested that this vaccine against human papillomavirus (HPV) can significantly reduce the likelihood of virus-related disease even for women who have had surgery for cervical cancer caused by HPV. Of 1,350 women who had undergone cervical surgery, 587 had previously received the HPV vaccine vs. 763 with a placebo, and those with the vaccine were 46% less likely to suffer subsequent HPV-related disease over the following two years.

- **KERYX BIOPHARMACEUTICALS and AETERNA ZENTARIS' perifosine (KRX-0401)** – The companies said this AKT inhibitor did not improve survival in a Phase III study in colorectal cancer (CRC).

- **MERCK KGAA's Erbitux (cetuximab)** – A study published in the ***Journal of the American Medical Association (JAMA)*** found this EGFR inhibitor was no better than chemotherapy alone for improving three-year disease-free survival (DFS) in patients with Stage III resected CRC – 67%-75% vs. 65%-72%. Furthermore, toxicity was higher with Erbitux.

- **NAVIDEA BIOPHARMACEUTICALS' Lymphoseek (99m-Tc-tilmanocept)** – The PDUFA date for this radioactive agent used to trace lymph nodes in cancer patients was extended by three months to September 10, 2012.

- **NOVO NORDISK's Levemir (insulin detemir)** – The FDA changed the label for this diabetes drug to a pregnancy Category B, which means it does not increase risk to the fetus.

- **REGENERON PHARMACEUTICALS and SANOFI's Zaltrap (aflibercept)** – A Phase III trial in prostate cancer missed the primary endpoint, failing to show a survival benefit. The drug is currently under priority review by the FDA in colon cancer, with a PDUFA date of August 4, 2012.

- **ROCHE/GENENTECH's Avastin (bevacizumab)** – Another batch of fake Avastin – 12 vials this time – was discovered, labeled as **Altuzan**, the authentic product's Turkish brand name. The fake Avastin reportedly entered the U.S. through a U.K. distributor, **Richards Pharma**, which also does business as **Richards Services**, **Warwick Healthcare Solutions**, and **Ban Dune Marketing**.

- **SENTARA MEDICAL GROUP** is stopping distribution of free drugs completely. *The question is whether other pharmas will follow suit.*

- **SHIRE's Lialda (mesalamine)** failed in a 592-patient Phase III trial in diverticulitis that the company had hoped would lead to a new indication, and Shire is giving up on efforts to expand the indication.

- **THERAVANCE's Relovair (fluticasone furoate and vilanterol trifenatate)** – **GlaxoSmithKline** upped its investment in Theravance to support this investigational agent for chronic obstructive pulmonary disease (COPD), which is expected to be submitted to regulators this year.

- **VIIV HEALTHCARE's dolutegravir** – In a 48-week Phase III trial, this QD integrase inhibitor was non-inferior to **Merck's Isentress** (raltegravir), which is BID (viral suppression 88% vs. 85%).

## NEWS IN BRIEF

### ASTELLAS PHARMA's mirabegron (YM-178) – FDA panel recommends approval

The FDA's Reproductive Health Drugs Advisory Committee voted 7-4 (with one abstention) that Astellas' mirabegron, an extended-release, once-daily tablet, should be approved to treat overactive bladder (OAB). The panel also voted:

- 8-4 that mirabegron is effective, reducing the number of times patients were incontinent.
- 9-3 that it is safe but that a postmarketing study should be required to better understand the side effects, particularly an increase in heart rate and blood pressure, hypersensitivity reactions (ranging from rash to anemia), increases in liver enzymes, urinary tract infections, and possibly malignancies.

### Bisphosphonates – linked to eye problems

A study published in the ***Canadian Medical Association Journal*** found that first-time users of these osteoporosis drugs may be at increased risk for serious inflammatory eye disease. The researchers compared ~11,000 first-time oral bisphosphonate users with >920,000 non-users and found a rate per

10,000 person-years of 29 cases of uveitis and 63 cases of scleritis (vs. 20 and 36 for non-users). The principal investigator, Mahyar Etminan, PharmD, from the University of British Columbia said, "The unanswered question is whether the risk of uveitis and scleritis is different with each individual bisphosphonate."

### Fluoroquinolones – risk of retinal detachment

A study published in ***JAMA*** linked these antibiotics – e.g., **Cipro** (ciprofloxacin), **Floxin** (ofloxacin), and **Noroxin** (norfloxacin) – to a small risk of retinal detachment as well as other previously known eye problems, including corneal perforations, optic neuropathy, and retinal hemorrhages. Over eight years, patients visiting an ophthalmologist who had a current prescription for a fluoroquinolone were 4.5 times more likely to have a retinal detachment than non-users, but the absolute risk was low (3.3% in current users vs. 0.6% in non-users), and the number needed to harm (NNH) was 2,500. The Canadian researchers found no increased risk after patients discontinued the antibiotic.

### JOHNSON & JOHNSON/JANSSEN ALZHEIMER IMMUNOTHERAPY/ELAN PHARMACEUTICALS' bapineuzumab – may work differently than previously thought

A report published in the ***Archives of Neurology*** found that this investigational antibody may reduce the development of tau tangles in the brain. A pooled analysis of two studies with a total of 46 patients found that bapineuzumab significantly reduced the level of phosphorylated tau (P-tau) in the cerebrospinal fluid (CSF) of patients with mild-to-moderate Alzheimer's disease (-9.9 pg/mL vs. 0 for placebo, p=0.03), which ***could*** mean it lowers levels in the brain and ***could*** mean that it reduces tau tangles in the brain. However, there was no change in CSF levels of amyloid beta, the protein that bapineuzumab is supposed to target for removal in the brain.

### NOVARTIS' QVA-149 (indacaterol 110 µg + glycopyrronium bromide 50 µg) – positive Phase III data in COPD

The company said this inhaled, once-daily, fixed-dose combination of the long-acting beta2-agonist indacaterol + a long-acting muscarinic antagonist (glycopyrronium bromide, NVA-237) met the primary endpoint in three Phase III trials in patients with COPD.

1. QVA-149 was significantly more effective than either of its components alone, than placebo, or than open-label tiotropium bromide (**Pfizer** and **Boehringer Ingelheim's Spiriva**) in increasing trough levels of $FEV_1$.
2. QVA-149 improved exercise endurance vs. placebo.
3. QVA-149 was shown to have a safety and tolerability profile similar to placebo.

Seven other trials are ongoing. Novartis said it will seek approval in Japan and Europe initially.

### SPECTRUM PHARMACEUTICALS

- **Apaziquone** failed to reduce the recurrence of tumors in a Phase III trial in non-muscle invasive bladder cancer (NMIBC).
- The company is buying **Allos Therapeutics**, which will give it the cancer drug **Folotyn** (pralatrexate).

## REGULATORY NEWS

### DEA strikes again in Florida

Now, **Cardinal** and its **CVS** pharmacies are not alone in the crosshairs of the Drug Enforcement Administration (DEA) over opioid dispensing. The DEA searched six Florida **Walgreens** stores and a Florida Walgreens distribution center in an effort to crack down on prescription opioid abuse.

### FDA seeking text-mining software

The FDA put out a request for proposal (RFP) seeking text-mining software that relies on natural language processing. The Center for Drug Evaluation and Research wants to use the software to analyze documents to find therapeutically useful and possibly unknown associations between drugs, disease processes, adverse events, and therapeutic agents. The FDA expects to choose a vendor by May 2012.

### Legislation introduced to standardize opioid tracking

A bipartisan group of House and Senate legislators – Rep. Hal Rogers (R-KY), Rep. Frank Wolf (R-VA), Sen. Rob Portman (R-OH), and Sen. Sheldon Whitehouse (D-RI) – introduced a bill (HR 4292) that would standardize how states share information about prescription drug trafficking. The legislation would link individual state prescription drug monitoring programs, allowing doctors to see if a new patient has a history of abuse in another state before issuing a prescription. The bill also would ease data sharing by creating uniform requirements for encryption and formatting.

### Measure proposed to speed FDA drug approvals

A draft proposal to be added to the FDA program reauthorization includes a proposal to expand the Agency's accelerated approval program and create a new "breakthrough" class for drugs that treat serious illnesses and show promise in early clinical trials to be better than existing therapies.

## FDA approvals/clearances

- **COOPERVISION's Avaira Toric silicone hydrogel (SiH) contact lens** was cleared, and the company plans to re-launch it in May. The lens was recalled last year due to an excess of silicone oil on the lens, which caused patient discomfort.
- **GENII's gi4000 electrosurgery generator**, a customizable generator designed to make it easier for doctors to perform GI surgery, was given 510(k) clearance.
- **SIEMENS HEALTHCARE's Somatom Definition Flash CT device** was cleared for use in combination with the company's **Stellar Detector**.
- **STERIS' Verify Spore Test Strip**, an optional accessory part to the company's System 1E device used to sterilize heat-reactive medical tools, was cleared for use.
- **UCB PHARMA's Neupro (rotigotine transdermal) –** This once-daily dopamine agonist patch was given expanded approval to treat advanced Parkinson's disease (PD) and moderate-to-severe restless legs syndrome (RLS).

## FDA recalls/warnings

- **INTELLICELL BIOSCIENCES** received an FDA warning letter for promoting its stem cell treatments for unapproved uses. The FDA said IntelliCell markets the products as biologic drugs, but they are not FDA approved as biologics.
- **LUITPOLD PHARMACEUTICALS/AMERICAN REGENT's cyanocobalamin injection –** Three lots were recalled due to cracks in the vials.
- **ST. JUDE MEDICAL's QuickSite and QuickFlex –** More lead problems for St. Jude, this time with these left heart leads for CRT devices that, like **Riata** defibrillator leads, have silicone insulation with the potential for externalized conductors. About 171,000 have been sold. The company claims there have been no electrical abnormalities, loss of pacing therapy, or deaths associated with this issue, but St. Jude has stopped selling both. The reported externalization rate is 0.023% but is likely in the 3%-4% range. St. Jude is not recommending extraction at this point.
- **SMITHS MEDICAL's CoZmonitor –** The company voluntarily recalled these glucose monitors because of a shortage of test strips that can be used with them.
- **THORATEC's HeartMate II left ventricular assist system (LVAS) –** The FDA made the already announced problem with kinking of the proximal flow graft a Class I recall, the most serious type of recall. The problem is not new; the level was just upgraded. HeartMate II devices have not been taken off the market.

## European regulatory actions

- **DELCATH SYSTEMS' Chemostat**, a second-generation hemofiltration cartridge, was granted a CE Mark. The product allows doctors to use the Chemostat device for percutaneous intra-arterial delivery of melphalan hydrochloride to the liver of patients.
- **ELEKTA's Agility**, a beam-shaping system used in Europe with linear accelerators, was granted a CE Mark.
- **QUIDEL's Tox A/B assay** received a CE Mark to identify toxin-producing *Clostridium difficile*.
- The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks will evaluate the risks of medical devices that use nanomaterials and submit feedback by March 2013, which the commission will use for labeling, risk categorization, and device instruction.
- The European Medicines Agency tightened its conflict-of-interest policy to ensure that its management, staff, and advisors have limited ties with pharmas.
- **Metal-on-metal hip implants –** The U.K.'s Medicines and Healthcare Products Regulatory Agency wants a ban on use of two hip implant products – **Johnson & Johnson/DePuy/Finsbury's Mitch TRH** cup/heads and **Stryker's Accolade** femoral stems. The Agency said patients getting a combination of these products have an "unacceptably high" rate of follow-up operations and should be closely monitored.

  In related news, a British registry found that the metal ions shed by these implants do not appear to cause cancer over the mid-term and, in fact, tended to be associated with a slightly *lower* risk of developing any type of cancer out to 7 years.

**Metal-on-Metal Hips and Cancer in British Registry**

| Measurement | Metal-on-metal hips | All hip replacements |
|---|---|---|
| Hematologic cancer | 0.92% | 1.21% |
| Malignant melanoma | 0.21% | 0.26% |
| Prostate cancer | 1.92% | 2.68% |
| Renal cancer | 0.53% | 0.71% |

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

- **AMGEN's Xgeva (denosumab)** – In a preliminary decision, NICE said this drug to treat bone metastases in breast and prostate cancer patients should be offered to the National Health Service, but at a discounted price.
- **BAYER and JOHNSON & JOHNSON's Xarelto (rivaroxaban)** – After getting more information from the companies on the clinical efficacy and cost-effectiveness of this anticoagulant, NICE recommended coverage to prevent stroke in atrial fibrillation patients.

## Regulatory news from other countries

***Japan:*** **ACTELION PHARMACEUTICALS' Brazaves (miglustat)**, sold as **Zavesca** elsewhere, was granted approval by the Ministry of Health, Labour, and Welfare to treat Niemann-Pick type C disease.

| 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 11 | **U-Systems' Automated Breast Ultrasound (ABUS) scanning device** for breast cancer detection in asymptomatic dense-breasted women | FDA's Radiological Devices Advisory Committee |
| April 12 | Possible reclassification of **breast transilluminators**, which are currently pre-amendment Class III devices, and **blood irradiators** | FDA's Radiological Devices Advisory Committee |
| April 17 | **Vivus' Qnexa** (phentermine + topiramate) for weight loss | PDUFA date for resubmission |
| 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 22-23 (?) | **Bristol-Myers Squibb's Eliquis** (apixaban), an anticoagulant for prevention of stroke in AFib, and **Johnson & Johnson's Xarelto** (rivaroxaban), an anticoagulant for a supplemental indication in acute coronary syndrome (ACS) | FDA's Cardiovascular and Renal Drugs Advisory Committee (*Neither of these is official yet. It may be that Eliquis is May 22 and Xarelto May 23, but this is not certain.)* |
| 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 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 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 | ***New*** 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 |