TRENDS-in-MEDICINE

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# 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 coverage of the **Transcatheter Cardiovascular Therapeutics** (TCT) meeting in Miami Beach.

## SHORT TAKES

- **ACCELRYS** acquired privately held **Aegis Analytical**, which offers enterprise manufacturing process intelligence solutions for compliance-intensive industries.

- **ACTELION's Opsumit (macitentan)**, an oral dual endothelin receptor antagonist (ERA), was submitted to the FDA to treat pulmonary arterial hypertension (PAH). In addition, the results of the double-blind, 742-patient, nearly 2-year Phase III SERAPHIN outcomes study were presented at the CHEST meeting of the American College of Chest Physicians (ACCP) in Atlanta. In that study, once-daily macitentan 10 mg provided a significant and clinically meaningful reduction in the risk of morbidity and mortality, reducing the risk by 45% vs. placebo ($p<0.0001$).

- **ARIAD PHARMACEUTICALS' ponatinib**, an investigational drug for treatment-resistant leukemia, was granted six-month priority review by the FDA. The PDUFA date is March 27, 2013.

- **BAYER's riociguat**, an oral soluble guanylate cyclase (sGC) stimulator, met the primary endpoint in the 12-week, 445-patient Phase III PATENT-1 trial in PAH, showing a statistically significant improvement in the six-minute walk distance (6MWD) of 36 meters vs. placebo. Both naïve and endothelin-receptor antagonist-experienced patients benefited.

- **CELGENE's pomalidomide** – The company said the independent data safety monitoring board (DSMB) conducted an interim analysis of this investigational treatment for relapse/refractory multiple myeloma and reported that it met the primary endpoint in the pivotal Phase III trial (MM-003), improving progression-free survival. In addition, the DSMB said that the combination of pomalidomide (a thalidomide analog) + low-dose dexamethasone had a better survival outcome than high-dose dexamethasone alone.

- **HOLOGIC's Selenia Dimensions** – The FDA's Radiological Devices Advisory Committee voted 9-1 to recommend approval of a new software module for this 3D mammography system to enable it to generate synthetic 2-dimensional images from the digital breast tomosynthesis data, thus obviating the need for acquiring full-field digital mammography images.

- **IRONWOOD PHARMACEUTICALS' linaclotide** – Ironwood signed a deal with **AstraZeneca** to jointly develop and sell this irritable bowel syndrome with constipation (IBS-C) drug in China.

- **JOHNSON & JOHNSON's Stelara (ustekinumab)** – A 526-patient Phase IIb study published in the ***New England Journal of Medicine*** found that this anti-IL12/23 was more effective than placebo in moderate-to-severe Crohn's disease that was resistant to TNF inhibitors, with significantly higher rates of clinical remission (41.7% vs. 27.4%) and response (69.4% vs. 42.5%) at Week 22.

- **LILLY's dulaglutide**, a once-weekly GLP-1 agonist for Type 2 diabetes, met the primary endpoint ($HbA_{1c}$ reduction) in three Phase III AWARD trials, and the company plans to submit it to the FDA in 2013. In one study, the company said, dulaglutide "worked better" than **Bristol-Myers Squibb** and **AstraZeneca's Byetta** (exenatide), and in another trial, it beat **Merck's Januvia** (sitagliptin), a DDP4 inhibitor.

- **MCKESSON** is buying Florida-based **PSS World Medical**, which distributes medical products to physician offices and long-term care homes.

- **MERCK's V710**, a *Staphylococcus aureus* vaccine developed to prevent surgical wounds from infection, failed to show a benefit – and may actually have increased mortality – vs. placebo in an ~4,000-patient study. In the trial, 201 vaccinated patients died vs. 177 with placebo (a rate of 5.7 vs. 5.0 per 100 person/years, p=0.20). Furthermore, vaccinated patients who did develop a staph infection were more likely to develop multiple organ failure (0.9 vs. 0.5 events per 100 person/years, p=0.04).

- **NEURONIX's neuroAD** – The company said that all six of the Alzheimer's disease patients treated so far in a Phase II trial of this computer-based device, which uses transcranial magnetic stimulation, have exhibited a significant improvement in cognition vs. a six-patient sham control. So far, the only adverse event with the device is a post-therapy headache, which was described as mild.

- **Oral contraceptives** – New recommendations issued by the American College of Obstetricians and Gynecologists (ACOG) warn oral contraceptives with drospirenone carry a slightly higher risk of blood clots than older oral contraceptives.

- **OREXIGEN THERAPEUTICS' Contrave (bupropion + naltrexone)** – The company said the FDA is open to "discussing options" for expediting review of this obesity drug.

- **STENTYS' Self-Apposing stent** received Investigational Device Exemption (IDE) approval from the FDA to conduct the APPOSITION-V trial, a pivotal, multinational, 1-year study in 880 STEMI patients vs. **Abbott's Multi-Link Vision**. The trial will begin in early 2013.

- **SVELTE MEDICAL SYSTEMS' Integrated Delivery System** – The FDA gave the green light for a 370-patient trial of this coronary stent delivery system that is designed to cut the cost and time to perform percutaneous coronary intervention (PCI).

- **TEVA's Treanda (bendamustine)** – The company said the FDA asked for more information on progression-free survival (PFS) before making a decision on an expanded indication for this chemotherapy treatment for indolent B cell non-Hodgkin's lymphoma.

- **THERAVANCE's TD-1211** – Data presented at the American College of Gastroenterology meeting indicated that this investigational mu opioid antagonist was effective, providing durable relief from opioid-induced constipation in patients with chronic pain without interfering with pain control.

- **Transplant drugs** – University of Cincinnati researchers plan to use a $2.7 million FDA grant to study whether there is a difference between **Fujisawa Pharmaceutical's Prograf** (tacrolimus) and generic drugs for liver and kidney transplant patients.

- **UNITED THERAPEUTICS' treprostinil diethanolamine** was rejected by the FDA, which questioned the ability of the drug (an oral version of **Remodulin**) to slow disease progression or have a meaningful impact on six-minute walk distance. The FDA recommended the company consider a fixed-dose design and more frequent dosing – if it decided to conduct another study. The company said it was not giving up on the drug.

## NEWS IN BRIEF

### Hydrocodone products – FDA recommends they remain Schedule III

The FDA recommended that hydrocodone-containing combination products – e.g., **Abbott's Vicodin** (hydrocodone + acetaminophen) – be kept as Schedule III controlled substances and ***not*** moved to Schedule II, which would impose tighter regulations to prevent abuse.

In briefing documents prepared for the October 29-30, 2012, meeting of the FDA's Drug Safety and Risk Management Advisory Committee, the FDA noted that there is not enough evidence to support the Drug Enforcement Administration's finding that hydrocodone-containing products have a similar abuse potential as Schedule II drugs and should be regulated as Schedule II. While the FDA staff said their analyses found that the hydrocodone products are "widely abused," they also said there is no objective threshold to correlate levels of abuse with the level of scheduling.

### Prostate cancer – possible treatment monitoring test

A proof-of-concept study published in ***Cancer Discovery*** found that a non-invasive blood test that measures androgen receptor signaling in the blood can help monitor treatment response to androgen-deprivation therapy in patients with metastatic castration-resistant prostate cancer (mCRPC). In addition, the researchers found that the assay was effective in tracking response to **Medivation** and **Astellas' Xtandi** (enzalutamide, MDV-3100).

That is, patients treated with Xtandi who had an increase in circulating tumor cells with androgen receptor signaling turned on had decreased overall survival. *This test could help doctors know when to switch among the several new drugs for mCRPC.*

### ST. JUDE MEDICAL – gets FDA 483 letter

St. Jude received a warning letter (a 483 letter) from the FDA following an inspection of its Sylmar CA plant where the Reata ICD leads were made. The letter cited 11 deficiences:

1. Process validation
2. Design verification
3. Design validation (in canines)
4. Design change
5. Design history
6. Training
7. CAPA system
8. CAPA procedures
9. Complaints
10. Document control
11. Control of inspection, measuring, and test equipment

While these look unrelated to the devices, they suggest a pattern of failure to follow through. What the FDA does next is likely to depend on:

a. How much the FDA thinks the Reata problem got out of hand (became too common) because St. Jude failed to follow through on some of the design issues that were cited.

b. How upset the FDA is more generally with St. Jude over Reata (or anything else).

c. How St. Jude responds in its by-November-7 response. If St. Jude is very aggressive and compliant in that response – and if the FDA is not out to "punish" St. Jude for the Reata problem – then this will be a normal 483 action without serious consequences for other approvals.

However, if the FDA thinks that these types of problems are endemic to St. Jude and, therefore, to other plants, ***and*** if the FDA is really upset over Reata and St. Jude's handling of the issues related to Reata, then this could be the beginning of a long haul fix for St. Jude.

St. Jude can probably handle this without a shutdown on approvals – if they do it correctly. But the potential is there for this to become much more serious. Remember what happened with Lilly a few years ago when computer systems at one plant then became a systemic Lilly problem and took years to resolve.

If St. Jude properly responds to this, it is most likely very manageable. But big pharma (and big device companies) don't always do that.

### TAKEDA/MILLENNIUM's vedolizumab – positive results in Crohn's disease

This gut-selective alpha-4 beta-7 integrin (a4β7) inhibitor met the primary endpoint in the maintenance part of a Phase III study that was presented at the American College of Gastroenterology meeting, providing long-term improvement in treatment-refractory Crohn's disease patients. At Week 52:

- 36.4% (100 mg) and 39.0% (50 mg) of vedolizumab patients achieved clinical remission vs. 21.6% of placebo patients.
- 43.5% and 45.5% of vedolizumab patients vs. 30.1% of placebo patients had a ≥100-point improvement in the Crohn's Disease Activity Index (CDAI).
- 31.7% and 28.8% of vedolizumab patients vs. 15.9% of placebo patients achieved corticosteroid-free remission.

### Vaccines

- **Flu vaccines.** Studies presented at Infectious Diseases (ID) Week in San Diego found that flu vaccines with four strains of the virus, instead of just three, were as safe as standard trivalent vaccines, and efficacy was non-inferior. Both **Sanofi** and **GlaxoSmithKline** have quadravalent vaccines in development.

  **Novartis**' flu vaccines were banned in several countries, including Austria, France, Germany, Italy, Spain, Switzerland, and Canada, after the company informed authorities in those countries of a buildup of particles in the shots, though no patient adverse events have been reported. Italy also demanded additional testing.

- **Pertussis vaccines.** **Kaiser Permanente** data presented at ID Week found that the acellular pertussis whooping cough vaccine (DTaP) is significantly less effective in preventing whooping cough than the whole-cell vaccine

(DTwP) that it replaced. There were 249 cases among the patients who got all five doses of the acellular vaccine vs. 12 cases among patients who received the whole-cell pertussis vaccine – an 8.57-fold increase in the relative risk of pertussis ($p<0.0001$). Getting a sixth acellular vaccine didn't help much; there was still a 3.55-fold increase in relative risk ($p<0.0001$) vs. the whole-cell vaccine.

- **PFIZER's Prevnar 13.** Speaking at the ID Week meeting, Matthew Moore, MD, of the Centers for Disease Control and Prevention (CDC) said that this pneumonia vaccine appears to have significantly reduced the incidence of the disease, including a 50%-60% drop among children age <2.

### Warfarin – adherence issues confirmed

A population-based cohort study in Canada, published in the ***Archives of Internal Medicine***, found that 61% of older patients in Ontario who were on warfarin therapy for atrial fibrillation (AFib) stopped treatment within five years, with a median time to discontinuation of 2.9 years. Other findings included:

- 8.9% did not fill a second prescription, 31.8% stopped therapy within a year, and 43.2% stopped within 2 years.
- Men stopped after a median of 2.6 years and women after 3.2 years ($p<0.001$).
- Patients age 66-75 took warfarin for a slightly shorter time (2.7 years vs. 3.1 years for patients >age 85).

## REGULATORY NEWS

### FDA adds eight drugs to safety watch list

The FDA raised a yellow warning flag about eight more drugs, putting them on its watch list due to new safety concerns from reports to the FDA Adverse Event Reporting System (FAERS) database in April, May, and June 2012. These were:

- **Codeine sulfate** – respiratory depression or arrest, leading to deaths in children taking codeine who are CYP2D6 ultra-rapid metabolizers.
- **Daiichi Sankyo's Benicar** (olmesartan medoxomil), an anti-hypertensive – malabsorption resulting in severe diarrhea and weight loss.
- **Fluoroquinolones** – retinal detachment.
- **Johnson & Johnson's Zyrtec** (cetirizine) – oculogyric crisis.
- **Proton pump inhibitors** – pneumonia.
- **Roche's Lariam** (mefloquine hydrochloride) for malaria – vestibular disorder.
- **Sanofi's Taxotere** (docetaxel) for chemotherapy – interaction with Sanofi's **Multaq** (dronedarone).
- **UCB's Keppra** (levetiracetam) – potential for drug abuse, misuse, or dependence.

### FDA approvals/clearances

- **EISAI's Fycompa (perampanel)** was approved to treat partial-onset seizures in patients with epilepsy age ≥12 years.
- **INSIGHTEC's ExAblate**, an MRI-guided ultrasound device for treating bone metastases pain in patients who were non-responsive to radiation or not a candidate for radiation, received premarket approval. It was already cleared to treat uterine fibroids.
- **NUVASIVE's PCM Cervical Disc System**, a motion-preserving total disc replacement device, was cleared for use.
- **SPINESMITH's VisuALIF**, a challenging access plate device, was cleared for use in anterior fixation solutions.
- **TEVA's Synribo (omacetaxine mepesuccinate)** was approved to treat adults with chronic myelogenous leukemia (CML).

### FDA recalls/warnings

- **ALERE** received an FDA warning letter citing violations of good manufacturing practices at the diagnostic device manufacturer's San Diego CA plant.
- **HEARTSINE TECHNOLOGIES' Samaritan 300/300P PAD public access defibrillators** – The company initiated a voluntary global correction to address two separate issues that may affect the ability to deliver therapy to a patient in a sudden cardiac arrest event.
- **JOHNSON & JOHNSON/ETHICON ENDO-SURGERY's Proximate and Transtar staplers** – The company began a Class I recall of these devices, which are used in the surgical treatment of prolapse and hemorrhoids, etc., because of difficulty users report in firing them, resulting in incomplete firing stroke and incomplete staple formation.
- **ST. JUDE MEDICAL** got a 483 letter about deficiencies at its Sylmar CA plant (*see News in Brief for details*).
- **STRYKER's Neptune Rover Waste Management Systems** – The recall has been upgraded to a Class I recall.

## European regulatory news

- **BAYER and JOHNSON & JOHNSON's Xarelto (rivaroxaban)** – The European Medicines Agency (EMA) recommended approval of this blood thinner for treatment and prevention of pulmonary embolism (PE) and prevention of recurrent deep vein thrombosis (DVT).
- **DELCATH SYSTEMS' ChemoSat**, an organ-isolating chemotherapy device, received a CE Mark for a new indication – delivering doxorubicin hydrochloride.
- **NOVO NORDISK's Tresiba (insulin degludec)** – The EMA's Committee for Medicinal Products for Human Use (CHMP) recommended approval of this long-acting insulin analog.
- **PFIZER's Xalkori (crizotinib)** was granted conditional marketing authorization by the European Commission to treat ALK+ non-small cell lung cancer.
- **ROCHE** – The EMA is conducting a first-of-its-kind probe into whether Roche Holding properly reported adverse events for all of the 19 drugs it markets in the European Union. There is already an ongoing investigation of Roche's failure to evaluate 80,000 reports of potential safety issues, so now Roche is involved in two EMA investigations. The EMA has until April 14 to make a recommendation to the European Commission on the marketing investigation.
- **Team-NB**, an association of medical device notified bodies in Europe, updated its code of conduct to include a requirement for unannounced medtech inspections at least once every three years. The requirement, which still must be finalized, would revise the current regulatory framework for medical devices and *in vitro* diagnostics.
- **VIVUS' Qsiva (phentermine + topiramate extended-release)** – As expected, the EMA followed the advice of CHMP and rejected this obesity drug, citing concerns about negative cardiovascular and nervous system effects from long-term use. The company said it would appeal the decision.

## Regulatory news from other countries

- ***Canada:***
  - **Methotrexate** – Health Canada warned against concomitant use of proton pump inhibitors and methotrexate, saying the combination can cause adverse events.
  - **Orphan drugs** – Health Canada is seeking public input on proposals to improve access to orphan drugs as well as increase research and development of the treatments. The Agency is developing a new framework for monitoring, approving, and designating orphan drugs.
- ***Greece:*** Greece suspended exports of all medications in order to address an internal drug shortage.

| Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*) | | |
|---|---|---|
| **Date** | **Topic** | **Committee/Event** |
| **2012** | | |
| October 29 | **Cornerstone Therapeutics/Cardiokine Biopharma's Lixar** (lixivaptan, CRTX-080) to treat hyponatremia | PDUFA date |
| October 29-30 | Discussion of benefits, risks, and abuse of drugs containing **hydrocodone** | FDA's Drug Safety and Risk Management Advisory Committee |
| November 1 | **CoAxia's NeuroFlo** catheter for treating cerebral ischemia | FDA's Neurological Devices Advisory Committee |
| November 7 | **Novartis' Signifor** (pasireotide) to treat Cushing's disease | FDA's Endocrinologic and Metabolic Drugs Advisory Committee |
| November 8 | **Novo Nordisk's Tresiba** (degludec) **and Ryzodeg** (degludecPlus) | FDA's Endocrinologic and Metabolic Drugs Advisory Committee |
| November 9 | **MSD Consumer Care's "Oxytrol for Women,"** an over-the-counter transdermal oxybutynin to treat overactive bladder in women | FDA's Non-prescription Drugs Advisory Committee |
| November 14 | Optimization of outcomes with **ventricular assist devices** (VADs) for patients with heart failure | CMS' MEDCAC |
| November 21 | **Pfizer's tofacitinib**, an oral JAK inhibitor for rheumatoid arthritis | PDUFA date (extended from August 21) |
| November 28 | **Johnson & Johnson's bedaquiline** to treat patients with multi-drug resistant pulmonary tuberculosis | FDA's Anti-infective Drugs Advisory Committee |
| November 28 | Discussion of the use of **absorbable material** in a variety of medical devices | FDA Workshop on Absorbable Medical Devices: Lessons Learned From Correlations of Bench Testing and Clinical Performance |
| November 29 | **Exelixis' cabozantinib** to treat medullary thyroid cancer | PDUFA date |
| December 4 | Discussion (no votes) of pediatric development plans for **GlaxoSmithKline's trametinib, Threshold Pharmaceuticals' TH-302, Boehringer Ingelheim's volasertib** (BI-6727)**,** and **Amgen's blinatumomab** (MT-103) | FDA's Pediatric Oncology subcommittee of the Oncologic Drugs Advisory Committee (ODAC) |
| December 15 | **Human Genome Sciences' raxibacumab** to treat anthrax | PDUFA date |
| December 20 (tentative) | **Hemispherx Biopharma's Ampligen** (poly I: poly C12U) to treat chronic fatigue syndrome (CFS) | FDA's Pulmonary-Allergy Drugs Advisory Committee (not confirmed) |
| December 21 | **Alexza Pharmaceuticals' Adasuve** (loxapine) for agitation associated with schizophrenia or bipolar disorder | PDUFA date |
| December 29 | **Aegerion Pharmaceuticals' lomitapide** to treat homozygous familial hypercholesterolemia | PDUFA date |
| December 29 | **Johnson & Johnson's bedaquiline** to treat multi-drug resistant tuberculosis | PDUFA date |
| December 30 | **NPS Pharmaceuticals' Gattex** (teduglutide) for short bowel syndrome | PDUFA date |

| Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*) | | |
|---|---|---|
| **Date** | **Topic** | **Committee/Event** |
| | **2013** | |
| January 16 | **Santarus' Uceris** (budesonide) for ulcerative colitis | PDUFA date (extended from October 16, 2012) |
| January 17 | **NuPathe's Zelrix** (transdermal sumatriptan), a migraine patch | PDUFA date |
| January 21 | **Impax Laboratories' Rytary** (IPX-066) for Parkinson's disease | PDUFA date (extended from October 21, 2012) |
| January 29 | **Sanofi/Genzyme** and **Isis Pharmaceuticals' Kynamro** (mipomersen) for homozygous familial hypercholesterolemia | PDUFA date |
| January 30 | **Raptor Pharmaceutical's cysteamine bitartrate** delayed-release (RP-103) to treat nephropathic cystinosis | PDUFA date |
| February 2 | **Hemispherx Biopharma's Ampligen** (poly I: poly C12U) to treat chronic fatigue syndrome | PDUFA date |
| February 10 | **Celgene's pomalidomide** for relapsed/refractory multiple myeloma | PDUFA date |
| February 24 | **Dynavax's Heplisav** hepatitis B vaccine | PDUFA date |
| February 28 | **Lundbeck** and **Otsuka's aripiprazole depot** to treat schizophrenia | PDUFA date |
| March tba | **Johnson & Johnson's canagliflozin**, a SGLT2 inhibitor to treat Type 2 diabetes | PDUFA date |
| March 1 | **Zogenix's Zohydro** (extended-release hydrocodone) for chronic pain | PDUFA date |
| March 17 | **Bristol-Myers Squibb** and **Pfizer's Eliquis** (apixaban,) an oral anticoagulant to prevent stroke in atrial fibrillation patients | PDUFA date |
| **March 27** | **Ariad Pharmaceuticals' ponatinib** for treatment-resistant leukemia | PDUFA date |
| March 28 | **Biogen Idec's BG-12** (dimethyl fumarate) for multiple sclerosis | PDUFA date (extended from December 28, 2012) |
| April 11 | **Sanofi/Genzyme** and **Bayer's Lemtrada** (alemtuzumab) for multiple sclerosis | PDUFA date canceled because the FDA refused to accept the filing |
| April 29 | **Shire's Vyvanse** (lisdexamfetamine dimesylate), sNDA for ADHD treatment in children | PDUFA date |
| May 12 | **GlaxoSmithKline** and **Theravance's Breo/Relvar** (fluticasone furoate + vilanterol) to treat chronic obstructive pulmonary disease (COPD) | PDUFA date |
| May 31 | **DepoMed's Serada** (gabapentin extended-release), a hot-flash treatment | PDUFA date |
| July 28 | **Aveo Oncology** and **Astellas Pharma's tivozanib** to treat advanced renal cell carcinoma | PDUFA date |