TRENDS-in-MEDICINE

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by Lynne Peterson

Quick Takes

…Highlights from this week's news relating to drugs and devices in development that are not covered in other *Trends-in-Medicine* reports…

Trends-in-Medicine
Stephen Snyder, *Publisher*
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409
Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

SHORT TAKES

- **AIDS vaccine –** A follow-up study published in ***The Journal of Infectious Diseases*** reported that an AIDS vaccine trial that was stopped early confirmed not only that it didn't protect men, but the vaccine made it ***more*** likely, not less likely, that some of the men would become infected with HIV. Men who were not circumcised and who had previously caught a common cold caused by the same virus used to make the vaccine were 2-4 times more likely than other men to become infected if they got the vaccine.

- **Alzheimer's disease –** When a person has amyloid beta plaque in the brain but no cognitive deficits, it has been referred to as "pathological aging" and thought to be benign. A study by University of Florida and Mayo Clinic researchers, published in the journal ***Alzheimer's Research & Therapy***, debunks this idea. The researchers reported that pathological aging may simply be very early Alzheimer's.

- **ANDROMEDA BIOTECH's DiaPep277**, which is designed to prevent insulin-secreting beta cells from being destroyed in Type 1 diabetics, was granted orphan drug status.

- **BAVARIAN NORDIC's Imvamune –** The company said the U.S. Department of Health and Human Services (HHS) is supporting a >4,000-patient Phase III trial of this small-pox vaccine.

- **BAYER and ONYX's Nexavar (sorafenib)** failed in MISSION, a Phase III trial in advanced relapsed/refractory non-small cell lung cancer (NSCLC), showing no improvement in overall survival, though progression-free survival (PFS) was extended.

- **BOEHRINGER INGELHEIM's olodaterol –** The results of a randomized, double-blind, cross-over, monotherapy Phase II trial presented at the American Thoracic Society meeting showed that FEV_1 was significantly better with 5 µg QD than 2 µg BID, and 5 µg BID was better than 10 µg QD. Olodaterol, a long-acting ß2-agonist (LABA) delivered via the Respimat Soft Mist Inhaler, is in development to treat chronic obstructive pulmonary disease (COPD). No safety or tolerability issues were reported. A QD fixed-dose combination of olodaterol and tiotropium (Spiriva) is being tested in the Phase III TOviTO trial.

- **CARDIAC DIMENSIONS' Carillon Mitral Contour System –** In a 36-patient study reported at the Heart Failure Congress and simultaneously published in the ***European Heart Journal***, this implant – which is positioned and anchored in the coronary sinus/great cardiac vein to reshape the annulus around the mitral valve – improved symptoms in heart failure patients, significantly reducing left ventricular systolic and diastolic volume at 12 months. Patients also increased their six-minute walk distance by >100 meters at one year.

- **CELLDEX THERAPEUTICS' CDX-011 (glembatumumab vedotin)** – The company said a 122-patient trial in refractory breast cancer found that 19% of glembatumumab patients vs. 14% of patients on standard chemotherapy had tumor shrinkage. In patients with tumors with GPNMB expression, 32% saw shrinkage; and 36% of patients not sensitive to estrogen, progesterone, or HER2 had a response.

- **CHELSEA THERAPEUTICS' Northera (droxidopa)** – The company plans to resubmit Northera, an orphan drug to treat fainting and dizziness in Parkinson's patients, to the FDA next year using data from a modified Phase III trial (expanded from 160 patients to 200 patients). The FDA rejected Northera, expressing concern about the single-site study that had been submitted.

- **DAVITA** is buying **HealthCare Partners**, which runs medical groups and physician networks in Southern California, Central Florida, and Southern Nevada. DaVita CEO Kent Thiry said DaVita is focused on integrated care for specialized kidney care services.

- **Dialysis** – After receiving a complaint about alkali dosing efforts during hemodialysis using dialysate concentrates containing acetic acid and acetate, the FDA issued a warning to healthcare providers to consider potential sources of alkali that can contribute to elevated bicarbonate levels in patients undergoing hemodialysis.

- **Dysentery** – A rodent study published in the journal ***Nature Medicine*** found that an inexpensive arthritis medication – auranofin – may be able to fight amoebic dysentery. In mice and hamsters, auranofin was 10 times more effective than the best drug currently available.

- **INTERMUNE's Actimmune (interferon gamma-1b)** – The company sold the rights to this drug for chronic granulomatous disease (CGD) and severe, malignant osteoporosis to **Vidara Therapeutics International**. InterMune plans to use the money from the transaction to fund further development of **Esbriet** (pirfenidone), a treatment for idiopathic pulmonary fibrosis that is approved in Europe but was rejected by the FDA in 2010. The company is conducting a Phase III trial in the U.S. in hopes of overcoming FDA concerns.

- **KINEX PHARMACEUTICALS' KX-02** – Kinex licensed the rights in China, Taiwan, and Singapore to this oncology drug to **Xiangxue Pharmaceuticals**. The company plans to file an investigational new drug (IND) application with the FDA in 3Q12.

- **LILLY's dulaglutide** – The company said this once-weekly Type 2 diabetes drug met the primary endpoint in a Phase II non-inferiority trial, showing that systolic blood pressure and heart rate with dulaglutide was comparable to placebo – and it lowered HbA_{1c} significantly more than placebo at Week 16 and Week 26. The most common adverse events were diarrhea, nausea, and vomiting.

- **MEDICINOVA's MN-221** – This investigational asthma medication missed the primary endpoint in a second Phase II trial, failing to improve FEV_1 vs. placebo.

- **MEDIVATION and ASTELLAS PHARMA's enzalutamide (MDV-3100)**, an androgen receptor signaling inhibitor, was submitted to the FDA to treat castration-resistant prostate cancer (CRPC), and the companies are asking for priority review.

- **Omega-3 fatty acids** – A small study published in the journal ***Pediatrics*** found that omega-3 fatty acids were no better than placebo at reducing the severity of tics in children with Tourette's, though there was an improvement in the degree to which the tics bothered the kids.

- **PEREGRINE PHARMACEUTICALS' bavituximab** – The company reported that a 112-patient study found that bavituximab beat standard chemotherapy in second-line NSCLC. The drug failed to beat placebo in a first-line study.

- **PFIZER's Vyndaqel (tafamidis)** – The FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted 13-4 against recommending approval for the treatment of transthyretin familial amyloid polyneuropathy. However, the panel also voted 13-4 that the drug's effects on secondary endpoints in the pivotal trial – such as better lower-limb function in some patients – may provide enough evidence for the FDA to approve it since there are no other approved therapies for this disease.

- **Resveratrol** – The National Institute on Aging is funding a 26-center study to test resveratrol's safety and effects on memory and brain function in patients with mild-to-moderate Alzheimer's disease.

- **ROCHE's pertuzumab** – Roche announced that **Chugai Pharmaceutical** submitted a new drug application to Japan's Ministry of Health, Labour, and Welfare for the treatment of HER2-positive metastatic or recurrent breast cancer.

- **SANOFI's slit-trap** – The company plans to test this liver cancer drug in China and perhaps South Korea next year.

- **SERVIER's Procoralan (ivabradine)** – When heart failure patients cannot tolerate an optimum dose of beta blocker, adding this cardiotonic agent can reduce heart failure hospitalizations and cardiac death. That was the finding of the SHIFT study reported at the Heart Failure Congress and published in the ***Journal of the American College of Cardiology*** with an editorial that suggested ivabradine may be a good add-on drug to achieve heart rate reduction but is not a substitute for beta-blocker therapy.

- **SHANGHAI PHARMACEUTICALS HOLDING** is under investigation by securities regulators in China and Hong Kong over its acquisition of **Shanghai Asia Pioneer Pharmaceutical** and **Changzhou Kony Pharma**.

- **THERAVANCE's Vibativ (telavancin)** – The company licensed manufacturing of this antibiotic to **Hospira** for five years.

- **TOCRIS BIOSCIENCE's Dostinex (cabergoline)** – A 72-patient retrospective study, reported at the American Urological Association meeting, found that this dopamine receptor agonist (0.5 mg twice a week) improved anorgasmia in 69% of men and completely resolved it in 52%. Anorgasmia often has a psychological origin, but it can occur as a side effect of radical prostatectomy or drug therapy.

NEWS IN BRIEF

Bisphosphonates
– more evidence of link to atypical fractures

A new study published in the ***Archives of Internal Medicine*** concludes that bisphosphonate use is associated with an increased risk of atypical fractures of the femur, and the risk may increase with duration of therapy. The study examined 477 patients with fractures who were hospitalized at one center and found:

- 39 patients had atypical fractures, and 82% of them had been taking a bisphosphonate (for an average of 5.1 years).
- 438 patients had common fractures, and just 6.4% of those were taking a bisphosphonate (for an average of 3.3 years).
- 200 fracture-free patients (the control) had a 47% reduction in the risk of common fractures.
- The odds ratio of developing an atypical fracture vs. a classic fracture was related to length of bisphosphonate use.
- Bisphosphonates reduced the risk of a vertebral fracture by ≥70% and wrist fractures by 50%.

Risk of Atypical Fracture with Bisphosphonates

Years of use	Odds ratio of atypical fracture vs. classic fracture
<2 years	35.1
2-5 years	46.9
5-9 years	117.1
>9 years	175.7
Overall	35.2 (p<0.001)

INTUITIVE SURGICAL's da Vinci
– robotic assist adds cost

A retrospective study reported at the American Urological Association found that a robotic-assisted radical prostatectomy (RARP) costs 62% more than an open procedure, adding almost $6,000 to the cost. And the hospital (the University of Pittsburgh) lost ~$4,000 on each robotic procedure. Reimbursement is the same for both procedures, so to break even on robotic surgeries, the hospital estimated it would have to do 10 times as many procedures.

The study compared 115 robotic procedures to 358 open procedures. There was no difference in hospital length of stay.

Comparison of Robotic and Open Prostatectomies

Measurement	Robotic	Open
Operative time	258 minutes	144 minutes
Cost	$14,004	$8,610
Profit/loss	Loss $4,000	Profit $1,300
Nursing costs	$876	$2,307
Physician services	$761	$444
Surgery	$8,458	$4,006
Operating room supplies	$2,852	$417

JOHNSON & JOHNSON's Xarelto (rivaroxaban)
– thumbs down for ACS

The FDA's Cardiovascular and Renal Drugs Advisory Committee recommended against approval (4 Yes, 6 No, 1 Abstention) of this blood thinner to reduce the risk of secondary cardiovascular events in patients with acute coronary syndrome (ACS).

The FDA briefing documents made it look like it would be a slam dunk for J&J, and the FDA reviewer even recommended approval, but the panel was concerned about a lack of data on patient discontinuations and deaths as well as an increase in major bleeding in the ATLAS-2 trial. *However, the FDA generally considers a vote this close to be neutral.* The PDUFA date is June 29, 2012.

SORBENT THERAPEUTICS' CLP (cross-linked poly-electrolyte) – failed Phase II trial but not dead

In a 100-patient Phase II study reported at the Heart Failure Congress in Belgrade, Serbia, and published in the ***European Heart Journal***, this investigational compound missed the primary endpoint, failing to reduce potassium levels (a marker of fluid overload) in heart failure patients. However, researchers were encouraged because it reduced dyspnea and the severity of heart failure symptoms and raised functional capacity and quality of life, and they suggested that – because it acts like a diuretic without kidney excretion – it may be useful for heart failure patients with chronic kidney disease if additional trials reproduce those benefits. The trial found that:

- Patient-reported dyspnea improved moderately or markedly in 37% of CLP patients vs. 22% of placebo patients.
- ~10% of CLP patients had physician-assessed disabling dyspnea on exertion vs. ~30% with placebo at Week 8.

CLP is composed of a super-absorbent but indigestible polymer taken orally that picks up water and electrolytes like calcium and potassium on its way out. But taking it isn't easy – 30 pills/day! – and there are safety questions. The primary adverse event was abdominal discomfort, and four patients died in the CLP group (though none was considered drug-related) vs. none with placebo.

Stem cells for cardiology – take a step forward

Israeli researchers reported in the ***European Heart Journal*** that skin cells taken from advanced heart failure patients were able to be coaxed in the lab to regenerate into healthy, patient-specific heart muscle cells. In rats, the new heart cells successfully integrated with existing heart tissue. By generating cardiomyocytes from the patients who will subsequently receive them, two problems are solved: immune rejection and supply constraints. However, human clinical trials are still 5-10 years away.

Nicholas Mills, MD, of the U.K. commented, "This technology needs to be refined before it can be used for the treatment of patients with heart failure, but these findings are encouraging." Gabor Foldes, MD, PhD, of the U.K. raised several concerns, including: the diversity of heart muscle cells, lack of mature forms of heart muscle cells when grown in a culture dish, eliminating non-human components and retroviruses, the time the process takes, immunogenicity, and building 3D structures.

REGULATORY NEWS

FCC assigns RF spectrum for wireless medical devices

The Federal Communications Commission (FCC) voted to set aside 40 mHz of radiofrequency (RF) spectrum – the Medical Body Area Networks (MBANs) – for wireless medical monitoring devices. The FCC also is working with the FDA to streamline the approval of medical devices operating on the new network.

Senate passes bill reauthorizing FDA user fees – but House still has to act

The Senate voted 96-1 to approve legislation that would reauthorize the FDA user fee program. The Senate bill also:

- Allows the FDA to inspect more drug manufacturing facilities in China, India, and other countries.
- Gives the FDA new tools to combat drug counterfeiting and shortages.
- Raises pharma fees by 6%.
- Puts dangerous synthetic drugs on the DEA Schedule 1.
- Prevents the FDA from disclosing any information under the Freedom of Information Act (FOIA) relating to drug inspections from a foreign government agency.
- Directs the U.S. attorney general to establish uniform standards for the exchange of controlled substance and prescription information for the purpose of preventing diversion, fraud, and abuse.
- Requires an independent assessment of the FDA's review of drug applications.
- Provides greater protection for whistleblowers.

The Senate also rejected amendments that would have:

- Allowed cheaper prescription drug imports from Canada.
- Prevented generic and brand-name drug companies from entering into agreements to delay access to generic drugs.
- Prohibited FDA approval of genetically engineered fish unless the National Oceanic and Atmospheric Administration agreed with such approval.
- Revoked the exclusivity of certain entities that are responsible for violations of the Federal Food, Drug, and Cosmetic Act, the False Claims Act, and other certain laws.

Task force recommends against routine PSA screening

The U.S. Preventive Services Task Force made it official, recommending against routinely screening prostate-specific antigen (PSA) levels in men. When the task force issued a draft proposal like this in October 2011, there was a huge hue and cry, but the task force decided to formalize the recommendation anyway. The task force explained its decision in the ***Annals of Internal Medicine***, saying, "There is convincing evidence that the number of men who avoid dying of prostate cancer because of screening after 10 to 14 years is, at best, very small," and doctors should discourage it. The task force estimated that:

- ≥15% of PSA tests will trigger a biopsy, and up to a third of the biopsied men will suffer side effects (e.g., pain, fever, bleeding, infection) requiring medical attention.
- ~1 in 8 men will have a positive biopsy leading to surgery, radiation, or anti-androgen therapy.
- 1 in 200 men undergoing surgery will die within a month of the operation, with 1%-7% having a serious cardiac adverse event (e.g., stroke or myocardial infarction).
- 20%-30% of radiotherapy patients will develop incontinence and/or impotence.
- 40% of men undergoing anti-androgen therapy will develop erectile dysfunction.

Task force co-chairman Michael LeFevre, MD, a family practitioner from the University of Missouri Medical School, said, "When you stack up those harms, the tiny or zero benefits do not outweigh the risk." The task force recommendation doesn't prevent a doctor from offering a PSA test or a man from requesting one, but patients should understand the downside of testing, and free mass screenings offered by urology clinics and hospitals should stop.

FDA approvals/clearances

- **APNICURE's Winx Sleep Therapy System**, a device to treat obstructive sleep apnea, was approved, and the company plans to launch it in select markets this year.
- **BIOPTIGEN's Envisu Spectral Domain Ophthalmic Imaging System**, a hand-held optical coherence tomography (OCT) device, was cleared.
- **ETVIEW MEDICAL's VivaSight-DL** device, which is used to give surgeons continuous airway visualization during lung isolation procedures, received 510(k) clearance.
- **TELEFLEX's Arrow** peripherally inserted central catheter with Chloragard Technology was granted 510(k) clearance for an antithrombogenic claim.

FDA recalls/warnings

- **ALERE's Triage D-dimer, Triage BNP, and Triage** cardiology tests were voluntarily recalled due to quality control issues.
- **FRANCK'S PHARMACY** – ***All*** sterile human and veterinary compounded drugs from this facility have been recalled due to microorganisms and fungal growth found in the company's clean room.
- **HOSPIRA's Carpuject Pre-filled Cartridges** – The FDA issued a healthcare alert of the possibility of overfill of morphine and hydromorphone after getting complaints from healthcare providers. The issue is believed to be a manufacturing problem.
- **MOOG MEDICAL DEVICES GROUP's Curlin Intravenous Administration Sets** – The company announced a voluntary recall, saying the devices could cause desanguination (blood loss), an under-delivery of prescribed medication/fluid, or a potential delay in therapy.
- **PFIZER's Advil Liqui-Gels** – 650,000 units were recalled due to a "strong odor" reportedly caused by over-processed gelatin.

European regulatory actions

- **AXIOMED SPINE's Freedom** cervical spinal disc replacement system was granted a CE Mark.
- **HEARTWARE's HVAD** received expanded CE Mark approval for the use of this left ventricular assist device as destination therapy.
- The European Commission launched an Innovative Medicines Initiative to invest in NewDrugs4BadBugs, a research project to develop antibiotics for superbugs.

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

BAYER's Xarelto (rivaroxaban) passed the final stage of the NICE assessment process to prevent strokes and systemic embolisms in atrial fibrillation patients.

Regulatory news from other countries

Russia: **ITAMAR MEDICAL's WatchPAT** system, which is used to diagnose sleep disorders, was approved by the Russian Federation's Ministry of Healthcare.

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 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 electromagnetic waves to characterize human tissue and provides intraoperative information on a malignancy of the surface of *ex vivo* lumpectomy specimens	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	**Johnson & Johnson's Xarelto** (rivaroxaban) for acute coronary syndrome	PDUFA date
June 29	**Astellas Pharma's Betanis** (mirabegron) to treat overactive bladder	PDUFA date
	July 2012	
July 17	**Vivus' Qnexa** (phentermine + topiramate) for weight loss	PDUFA date (extended from April 17)
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 non-cancer pain	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)	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
	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