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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SHORT TAKES

- **ACORDA THERAPEUTICS' Ampyra (dalfampridine)** – Although the 10 mg BID dose is FDA approved to improve walking speed in multiple sclerosis (MS) patients, a 430-patient trial of a lower dose (5 mg BID) failed to show a benefit over placebo. The FDA had requested the low-dose study because of concerns about seizures with the approved dose. However, the 10 mg BID dose also didn't improve walking speed in the trial. *Now, what will the FDA do – withdraw approval of the 10 mg BID dose, request another high-dose trial, restrict use, nothing?*

- **AMGEN's Xgeva (denosumab)** – A study published in ***Clinical Cancer Research*** found that metastatic breast cancer patients had significantly fewer (p=0.0006) skeletal-related events (SREs) with Xgeva vs. **Novartis' Zometa** (zoledronic acid). The researchers also reported that Xgeva showed superiority to Zometa in preventing different types of SREs, including radiation to bone and hypercalcemia of malignancy.

- **Atypical antipsychotics** – A review of 114 studies by researchers at the Agency for Healthcare Research and Quality, published in the ***Annals of Internal Medicine***, found that the "newer, more expensive" antipsychotics are not noticeably better than first-generation antipsychotics in treating positive symptoms associated with schizophrenia.

- **BG MEDICINE's CardioScore** – The company withdrew its application to the FDA for approval of this cardiac diagnostic test, saying it could not meet the Agency's August 15, 2012, deadline for the required additional data but plans to resubmit the application when those data are available.

- **BIOVEST INTERNATIONAL's BioVaxID** – The company said the FDA is requesting a second Phase III trial before approving this personalized anti-idiotype vaccine to treat follicular non-Hodgkin's lymphoma and outlined how that trial should be conducted.

- **Blindness** – A study published in the ***Proceedings of the National Academy of Sciences*** found that blind mice had their vision restored with a device that helped diseased retinas send signals to the brain. The investigators hope to start human trials in one to two years.

- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran)** – A study published in the ***Journal of the American College of Cardiology*** found that the 150 mg BID dose of Pradaxa more effectively reduced the risk of stroke or systemic embolism in atrial fibrillation patients vs. **Johnson & Johnson's Xarelto** (rivaroxaban). However, there was no significant difference between low-dose (110 mg BID) Pradaxa vs. Xarelto. Neither dose of Pradaxa was more effective than **Bristol-Myers Squibb's Elquis** (apixaban).

- **Fluoroquinolones** – A population-based, case-controlled study published in the ***Canadian Medical Association Journal*** (CMAJ) found that hospitalization for idiosyncratic acute liver injury was rare but occurred more often in elderly patients (age ≥66) who were prescribed either of two common fluoroquinolones – moxifloxacin or levofloxacin vs. clarithromycin. The researchers estimated that liver problems concurred in 6 patients per 100,000 treated with the antibiotics.

- **GLAXOSMITHKLINE's Bosatria (mepolizumab)** – A trial found that this anti-IL-5 reduced the number of asthma attacks experienced by difficult-to-treat asthmatics. After 1 year, mepolizumab patients had 50% fewer severe outbreaks requiring an ER visit or hospitalization vs. placebo. Mepolizumab patients also had half as many outbreaks requiring oral steroids.

- **KV PHARMACEUTICAL's Makena (hydroxylprogesterone caproate injection)** – The company finally won a round. A judge in Georgia ruled that the state should offer Makena instead of using a compounded formulation because only Makena has FDA approval.

- **Male birth control** – Researchers at Dana-Farber Cancer Institute, writing in the journal ***Cell***, have identified a compound, JQ1 (a BET bromodomain inhibitor), that has promise as a male birth control pill. The drug was initially developed to treat cancer, but in a mouse study it acted as a form of male contraception. When the mouse took the drug, it reduced the number and quality of their sperm, but the sperm count rebounded when the drug was discontinued.

- **MEDIVATION and ASTELLAS' enzalutamide (MDV-3100)** – A study published in the ***New England Journal of Medicine*** found that this investigational prostate cancer drug improved survival (mean 18.4 months vs. 13.6 months with placebo), even in men refractory to other therapies. The researchers also reported that the drug showed superiority on every secondary endpoint, including PSA response, soft tissue response, quality of life, and time-to-PSA progression.

- **Multiple myeloma** – Researchers reported that myeloma cells have significantly increased levels of the bone-remodeling protein annexin A2 (ANXA2), which suggests a potential new drug target. A study published in ***Blood*** found that event-free survival was significantly lower in patients with high levels of ANXA2 expression, making it a negative prognostic factor.

- **NPS PHARMACEUTICALS' Gattex (teduglutide)** – The FDA delayed the PDUFA date for this investigational DPP-4 treatment for short bowel disease by three months to December 30, 2012.

- **PFIZER's tofacitinib** – A 194-patient, double-blind Phase II study published in the ***New England Journal of Medicine*** found that this investigational, oral rheumatoid arthritis drug reduced symptoms (pain and bleeding) in patients with moderate-to-severe ulcerative colitis, with 78% of patients at the highest dose (10-15 mg) reporting some relief and nearly half of those having a remission.

- **Robotic percutaneous intervention (PCIs)** – An online survey by ***CRTonline.com*** found that 71% of doctors do ***not*** believe in robotic PCI, 23% do believe in it, and 6% were unsure.

- **SANTARUS' Uceris (budesonide)** – The FDA delayed a decision (PDUFA date) for this investigational treatment for ulcerative colitis by three months, from October 16, 2012, to January 16, 2013.

- **SENSIMED's Triggerfish** – A 40-patient study published in the ***Archives of Ophthalmology*** found that continuous intraocular pressure measurement over 24 hours with this contact lens sensor was safe and tolerable with repeated use in glaucoma patients. However, mild adverse effects (e.g., blurred vision, conjunctival hyperemia, and superficial punctate keratitis) occurred in all but two patients, and the measurements were variable.

- **SSRIs** – A study published in the ***Journal of General Internal Medicine*** suggested that primary care doctors using electronic medical records (EMRs) may be less likely to prescribe antidepressants to patients with multiple comorbidities than doctors using paper medical records. The University of Florida researchers said they didn't know why this is happening but speculated that it could be due to reduced interaction between patients and physicians or an increased focus on physical issues. *If this study is accurate, there could be a drop in SSRI prescriptions as EMR use increases.*

- **TEVA's Quartette (ethinyl estradiol + levonorgestrel)** – The FDA accepted the new drug application (NDA) filing for this oral contraceptive.

- **VIROPHARMA's Vancocin (vancomycin)** – A study published in the ***Journal of the American Society of Nephrology*** found that vancomycin might not be the best antibiotic choice for treating patients with end-stage renal disease (ESRD) who develop methicillin-susceptible *Staphylococcus aureus* (MSSA). The study suggested that cefazolin is associated with a markedly lower risk of hospital admission or death.

NEWS IN BRIEF

ASTRAZENECA

- **Caprelsa (vandetanib).** A study by French researchers, published in ***The Lancet Oncology***, found that this kinase inhibitor extended survival by 37% in advanced differentiated thyroid cancer (to 11.1 months vs. 5.9 months with control). However, they also reported that the drug has "significant" toxicity, with 2 of 72 patients dying from a treatment-related adverse event – 1 hemorrhage from skin metastases and 1 pneumonia – vs. 1 death in the 73 placebo patients.
- **Nexium (esomeprazole).** AstraZeneca sold the over-the-counter (OTC) rights to this heartburn drug to **Pfizer**, which hopes to launch an OTC Nexium in 2014.

Beta-amyloid – does it or doesn't it lead to Alzheimer's?

Does beta-amyloid accumulation cause Alzheimer's, or is it a non-related association? The debate continues. The failure of **Pfizer's bapineuzumab** might suggest it isn't causative, but scientists are arguing that this can't be definitively concluded. Scientists reported in ***Nature*** that there is an APP gene mutation that is ***protective*** against Alzheimer's and might give new life to the beta-amyloid theory.

Researchers from **Genentech** and **deCODE Genetics** in Iceland found that a rare allele (occurring in ~1% of Icelanders and ~1:5,000 North Americans) reduces sporadic Alzheimer's disease risk and slows the rate of cognitive decline in elderly patients. They basically showed that reduced beta-amyloid can prevent even late-onset Alzheimer's. The finding also is a sort of proof-of-principle for BACE1 inhibitor development.

IDENIX PHARMACEUTICALS' IDX-184 – on clinical hold (*again*)

The FDA imposed a partial clinical hold on human trials of this NS5B nucleotide polymerase inhibitor for hepatitis C until the Agency is convinced the drug doesn't cause cardiac problems. In July, **Bristol-Myers Squibb** halted trials of its NS5B nucleotide polymerase inhibitor, BMS-986094, because a patient developed heart failure. Idenix claims there have been no heart-related side effects linked to its drug, but the FDA appears to be taking a very cautious approach to this drug class.

This is the second clinical hold for IDX-184. The FDA put a hold on trials in 2010 over liver concerns, but that hold was lifted in February 2012. The good news for Idenix is that the Phase IIb trial of IDX-184 was already completed before the clinical hold began, and no patients were currently being dosed with the drug. However, the FDA requested cardiac tests (including echocardiograms) on all 67 patients who were given IDX-184, and the company is trying to track down those patients.

Will the FDA also halt studies of other NS5B nucleotide inhibitors, such as Gilead Sciences' GS-7977 or Vertex and Alios BioPharma's ALS-2200 and ALS-2158?

ROCHE's high-sensitivity tropinin T (hs-cTnT) assay – algorithm predictive for AMI

A study found that this biomarker test – used with a specific algorithm – can quickly determine whether a patient presenting to the emergency room with chest pain is having an acute myocardial infarction (MI) or not. The researchers reported that a change from a baseline hs-cTnT measure and another taken an hour later was predictive of an MI. The algorithm was: A patient was negative for AMI with a baseline hs-cTnT <12 ng/L and an absolute change within the first hour of <3 ng/L or positive for AMI if there was a baseline hs-cTnT of ≥52 ng/L or an absolute change in the first hour of ≥5 ng/L.

In the patients in which this strategy was tried, researchers could rule out an MI in 60% of cases. The rule-out algorithm had 100% sensitivity and negative predictive value, and the rule-in algorithm had 97% specificity and 84% positive predictive value. And the in/out thresholds were not affected by sex, ECG features, or time from symptom onset.

ST. JUDE MEDICAL's Riata and Riata ST – FDA issues safety notice

The FDA reminded doctors that these implantable cardiac defibrillator (ICD) leads – which the company stopped selling in 2010 and which were recalled in November 2011 – have an increased risk of premature insulation failure that can impact the lead's ability to function properly, starting ~4 years after implant. Currently, ~79,000 Americans have one of these leads. The FDA recommended:

- Doctors notify patients who have a recalled lead and "closely monitor" them.
- Doctors examine patients (who have not had a recent evaluation and device interrogation) to see if there are any electrical abnormalities. This is a recommendation for proactive fluoroscopy screening of all Riata patients.
- Doctors consider remote monitoring of patients to better detect electrical abnormalities.

- St. Jude expand its postmarket surveillance studies to include Optim-coated Riata ST **Optim** and **Durata** leads and to include three years of follow-up.

In addition, the company recommended:

- Reprogramming the device to increase the chance for detection of a lead abnormality.
- Turning on the patient alert and remote monitoring alerts.

THROMBOGENICS' ocriplasmin – effective in vitreomacular adhesions

Two randomized, double-blind, sham-controlled Phase III studies (with 652 eyes), published in the ***New England Journal of Medicine***, found that a single intravitreal injection (125 µg) of this recombinant protease resolved vitreomacular adhesions better than a placebo injection.

Phase III Results with Ocriplasmin in Vitreomacular Adhesions

Measurement	Ocriplasmin	Placebo	p-value
Adhesion clearance	26.5%	10.1%	<0.01
Total posterior vitreous detachment	13.4%	3.7%	---
Non-surgical closure of macular holes	40.6%	10.6%	<0.001
Vitrectomy in first 6 months	17.7%	26.6%	0.02
BCVA gain of ≥3 lines	12.3%	6.4%	0.02
Improvement in quality of life	Better	----	0.007
Adverse events			
Adverse events (e.g., vitreous floaters, photopsia, eye pain, conjunctival hemorrhage) *	68.4%	53.3%	<0.001
Vitreous floaters	16.8%	7.5%	---

* Mostly transient and mild

REGULATORY NEWS

FDA wants pre-review of 510(k) applications

As part of its efforts to expedite medical device reviews, the FDA proposed establishing pre-review evaluations of applications for medical devices submitted for 510(k) clearance. Under the proposal, the Agency would notify firms within 15 days whether their 510(k) submissions are "administratively complete" or inadequate, and, if inadequate, what the missing factors are. The pre-review will not consider the quality of clinical data or deal with questions about submission quality, just "objective criteria."

FDA urged to update medical device-safety databases

Two Democratic legislators – Rep. Edward Markey (D-MA) and Sen. Jeff Merkley (D-OR) – sent a letter to the FDA, attempting to assess the agency's "willingness" to update its 510(k) database to "clearly indicate devices that have been recalled for design flaws that could affect safety or effectiveness." The legislators want the FDA to update the database within 30 days of completing a review of a manufacturer's root-cause analysis if it finds that the flaw triggering a recall was serious. They also want the FDA to ensure that the public is notified when a product repeats the same design flaw that caused a predicate's recall.

FDA approvals/clearances

- **BD DIAGNOSTICS' BD Max MRSA molecular assay**, which last month was cleared for use to identify patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA), received a Clinical Laboratory Improvement Amendments (CLIA) moderate complexity rating.
- **JARVIK HEART's Jarvik 2000** – The FDA said the company could begin a ≤350-patient, two-year study of this ventricular assist device in end-stage heart failure patients who are ineligible for a transplant.
- **PHARMALUCENCE's sulfur colloid injection** (SCI) was approved for use in determining the location of lymph nodes in patients with malignant melanoma. It was already approved to detect lymph nodes in breast cancer patients.
- **SANOFI and INTELLIJET's Auvi-Q**, an epinephrine auto-injector, was approved for emergency treatment of severe allergic reactions.
- **SIEMENS HEALTHCARE's syngo.PET Amyloid Plaque software** received FDA clearance for use in assessing patients for Alzheimer's disease. The software can now be used with PET and PET/CT scanners.
- **SPACELABS HEALTHCARE's Capnography Pod**, a sidestream gas analyzer that works with the company's qube patient monitor, was cleared for use as a non-invasive way to measure carbon dioxide concentration in gas mixtures.
- **STRYKER's Trevo Pro**, a blood clot retrieval device – using the Stentriever system from Concentric Medical – for treating ischemic strokes, received 510(k) clearance.

FDA recalls/warnings

- **HOSPIRA**
  - **Propofol** injectable emulsion was recalled due to glass particles in the vials.

- **Hydromorphone cartridge** for the **Carpuject** syringe system was voluntarily recalled due to possible overfill.

■ **ST. JUDE MEDICAL's Eon and Eon Mini** – The company is recalling these neurostimulation devices for pain management due to battery issues, but the company said it has found a fix for the problem.

European regulatory news

■ ***Germany:*** **BIONOR's Vacc-4x** – The government has approved a study of this immunotherapy in combination with **Celgene's Revlimid** (lenalidomide) to improve the immune systems of HIV patients.

■ ***Netherlands:*** **COSMO PHARMACEUTICALS' Cortiment (budesonide)** – The Dutch Regulatory Agency rejected this treatment for ulcerative colitis treatment, citing lack of "clinical relevance."

■ ***EMA:*** As part of its transparency push, the European Medicines Agency (EMA) has begun issuing evidence-based reports on ancillary therapeutic substances used with medical devices. The reports are expected to help medtech companies in their preparation of documentation for submission to notified bodies.

Regulatory news from other countries

■ ***China:*** **3SBIO's APX-001/SSS-07**, an investigational therapy for autoimmune and inflammatory diseases, was submitted to the Chinese State Food and Drug Administration. 3SBio developed the drug using Apexigen's monoclonal-antibody technology.

■ ***India:*** **PLURISTEM THERAPEUTICS' PLX (PLacental eXpanded) cells** – The Indian Ministry of Health and Family Welfare authorized a Phase II trial in patients with Buerger's disease.

■ ***Japan:*** **ASTRAZENECA and ASTELLAS PHARMA's Symbicort Turbuhaler (formoterol + budesonide)** – This dry powder inhaler combination of a long-acting beta agonist and a corticosteroid received expanded approval to treat chronic obstructive pulmonary disease (COPD). It was already approved to treat bronchial asthma.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	August 2012	
August 21	**Pfizer's tofacitinib**, an oral JAK2 inhibitor for rheumatoid arthritis	PDUFA date (but this probably will be delayed)
August 27	**Gilead Sciences' Quad** (emtricitabine+tenofovir+elvitegravir+cobicistat) for HIV	PDUFA date
August 28	**Discussion of reporting requirements** for Division of Cardiovascular Devices 30-day notices and annual reports	FDA public workshop
	Other 2012	
September tba	**Vivus' Qnexa** (topiramate + phentermine) for obesity	EMA oral hearing
September 5	**Salix Pharmaceuticals' Provir** (crofelemer) for HIV-related diarrhea	PDUFA date (extended from June 5)
September 5	**Novartis' tobramycin inhalation powder** for management of cystic fibrosis patients infected with *Pseudomonas aeruginosa*	FDA's Anti-Infective Drugs Advisory Committee
September 8	**Ironwood Pharmaceuticals and Forest Laboratories' linaclotide** for irritable bowel syndrome	PDUFA date
September 10	**Navidea Biopharmaceuticals' Lymphoseek** (tilmanocept), a radioactive agent for tracing lymph nodes in cancer patients	PDUFA date (extended from June 10)
September 13	**Cornerstone Therapeutics/Cardiokine Biopharma's lixivaptan** for treatment of symptomatic hypervolemic and euvolemic hyponatremia associated with heart failure and syndrome of inappropriate antidiuretic hormone (SIADH) and **West-Ward Pharmaceutical's phenylephrine hydrochloride injection** to increase blood pressure in acute hypotensive states (e.g., shock and peri-operative hypotension)	FDA's Cardiovascular and Renal Drugs Advisory Committee
September 21	Classification of posterior **cervical screws**, including pedicle and lateral mass screws	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
September 23	**Regeneron's Eylea** (aflibercept) for central retinal vein occlusion (CRVO)	PDUFA date
September 27-28	Regulatory science considerations for performance validation of **radiation biodosimetry** devices	FDA public meeting
September 28	**Second Sight's Argus II Retinal Prosthesis System** for severe to profound retinitis pigmentosa	FDA's Ophthalmic Devices Advisory Committee
October 12	**Celgene's Abraxane** (nab-paclitaxel) to treat NSCLC	PDUFA date
October 15	Need for and design of **clinical development programs** for approval of **parenteral lipid emulsion products** as nutritional support	FDA's Gastrointestinal Drugs Advisory Committee
October 17	**Aegerion Pharmaceuticals' lomitapide** to treat homozygous familial hypercholesterolemia	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
October 17	**ThromboGenics' ocriplasmin** to treat vitreomacular adhesions	PDUFA date
October 18	**Sanofi/Genzyme and Isis Pharmaceuticals' Kynamro** (mipomersen) to reduce cholesterol in patients with homozygous familial hypercholesterolemia	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
October 21	**Impax Laboratories' IPX-066** for Parkinson's disease	PDUFA date
October 29	**Cornerstone Therapeutics' CRTX-080** to treat hyponatremia	PDUFA date
October 29-31	**Bayer's regorafenib** for metastatic CRC	PDUFA date
November 8	**Novo Nordisk's Tresiba** (degludec) **and Ryzodeg** (degludecPlus)	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
November 14	Optimization of outcomes with **ventricular assist devices** (VADs) for patients with heart failure	CMS' MEDCAC
November 22	**Medivation** and **Astellas' enzalutamide** (MDV-3100) for castration-resistant prostate cancer	PDUFA date
November 29	**Exelixis' cabozantinib** to treat medullary thyroid cancer	PDUFA date
December 15	**Human Genome Sciences' raxibacumab** to treat anthrax	PDUFA date
December 21	**Alexa Pharmaceuticals' Adasuve** (loxapine) for agitation associated with schizophrenia or bipolar disorder	PDUFA date
December 28	**Biogen Idec's BG-12** for multiple sclerosis	PDUFA date
December 29	**Aegerion Pharmaceuticals' lomitapide** to treat homozygous familial hypercholesterolemia	PDUFA date
December 30	**NPS Pharmaceuticals' Gattex** (teduglutide) for short bowel disease	***New*** 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	***New*** PDUFA date (extended from October 16, 2012)
January 17	**NuPathe's Zelrix** (transdermal sumatriptan), a migraine patch	PDUFA date
January 29	**Sanofi/Genzyme and Isis Pharmaceuticals' Kynamro** (mipromersen) for homozygous familial hypercholesterolemia	PDUFA date
January 30	**Raptor Pharmaceutical's cysteamine bitartrate** delayed-release (RP-103) to treat nephropathic cystinosis	PDUFA date
February 10	**Celgene's pomalidomide** for relapsed/refractory multiple myeloma	PDUFA date
February 24	**Dynavax's Heplisav** hepatitis B vaccine	PDUFA date
March 1	**Zogenix's Zohydro** (extended-release hydrocodone) for chronic pain	PDUFA date
April 11	**Sanofi/Genzyme and Bayer's Lemtrada** (alemtuzumab) for multiple sclerosis	PDUFA date