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

NOTE: Subscribe to ***Trends-in-Medicine*** for coverage of the **FDA public hearing on opioid labeling** and the **Angiogenesis, Exudation, and Degeneration 2013** conference sponsored by Bascom Palmer Eye Institute in Miami.

SHORT TAKES

- **AERAS' MVA-85A** – A Phase IIb study in 2,800 South African HIV-negative infants, published in ***The Lancet***, found that this investigational tuberculosis vaccine was safe, but it failed to prevent new TB infections in infants. The non-profit company is hoping it will work in other patient populations. At three years, 32 vaccine patients got TB vs. 39 with placebo, an efficacy rate of ~17%.

- **ALNYLAM PHARMACEUTICALS and THE MEDICINES COMPANY** formed a strategic alliance to develop Alnylam's ALN-PCS RNAi, a therapeutic program targeting PCSK9 for lowering cholesterol.

- **Alzheimer's disease** – According to a study of 10,802 people in Chicago over 19 years, the number of people with Alzheimer's disease will triple by 2050, due to aging baby boomers, to 13.8 million – up from 4.7 million in 2010. About 7 million of these will be age ≥85. The study was supported by the Alzheimer's Association and the National Institute on Aging of the National Institutes of Health and was published in ***Neurology***, the medical journal of the American Academy of Neurology.

- **BIOGEN IDEC and ELAN's Tysabri (natalizumab)** – Biogen is buying out Elan's interest in this multiple sclerosis therapy – not buying Elan itself.

- **Cholesterol** – A National Institutes of Health study published in ***Hepatology*** identified a microRNA liver gene (miR-27b) that regulates lipid levels in the blood. In a related editorial, Carlos Fernández-Hernando, MD, from New York University School of Medicine, confirmed the emergence of microRNAs in regulating cholesterol and fatty acid metabolism. *Perhaps a new target for dyslipidemia therapy?*

- **Depression** – A six-week, 120-patient study published in ***JAMA Psychiatry*** found that using transcranial direct current stimulation (tDCS) of the brain along with a selective serotonin reuptake inhibitor – e.g., **Pfizer's Zoloft** (sertraline) – helped about two-thirds of patients with major depressive disorder (MDD) feel better. Used alone, tDCS efficacy was roughly comparable to Zoloft alone, but together, they did better.

- **D-PHARM's DP-b99** – A study published in ***Stroke*** found that this zinc-targeting chelating agent failed to improve outcomes in patients with acute ischemic stroke, and the trial was stopped early. At 90-days post-stroke, the modified Rankin score and mortality were similar for DP-b99 patients vs. placebo patients (p=0.21).

- **GALAPAGOS and GLAXOSMITHKLINE's GSK-2586184 –** GSK plans to start Phase II trials of this investigational JAK1 inhibitor in systemic lupus erythematosus (SLE) and psoriasis.

- **HEMISPHERX BIOPHARMA's Ampligen (rintatolimod, poly I: poly C12U) –** The FDA rejected this investigational drug to treat chronic fatigue syndrome (CFS), issuing a complete response letter that requested new data analyses, additional non-clinical trials, and at least one more clinical trial. This was not surprising since the FDA's Arthritis Advisory Committee voted 8-5 against recommending approval, citing questionable trial results. The company said it will meet with the FDA and may file a formal appeal. *Don't expect a positive outcome to the appeal.*

- **KYTHERA BIOPHARMACEUTICALS and BAYER's ATX-101 (synthetic sodium deoxycholate) –** Two Phase III European trials in a total of 723 patients, were presented at the International Master Course on Aging Skin (IMCAS) in Paris, showing that this injectable drug (at monthly doses of 1 or 2 mg/cm for up to 4 cycles) reduced submental (under-the-chin) fat deposits significantly better than placebo by clinician-reported measures. Subjective patient reports also indicated a reduction in the submental fat. *The question is whether cosmetic surgeons will see this as just more controversial mesotherapy.*

- **LILLY's tabalumab –** The company said it is stopping ***all*** trials of this investigational drug for moderate-to-severe treatment-resistant rheumatoid arthritis patients because it didn't work. An interim analysis of the first of three Phase III trials found that tabalumab was unlikely to show efficacy. However, tabalumab is still being tested in a Phase III trial in SLE and in a Phase II trial in multiple myeloma.

- **PFIZER's Sutent (sunitinib) –** A study in renal cell carcinoma patients, published in ***Cell Reports***, found that this oncology drug does ***not*** cause tumors to grow faster after treatment stops. The researchers concluded that no matter how long patients took the drug, it did not cause harm, did not speed up tumor growth, and did not shorten survival post-treatment.

- **Pharma –** A 4,341-person study funded by **Lilly** found that people believe that big pharma is more interested in treating cancer than in curing it. *It looks like the Pharmaceutical Research and Manufacturers of America (PhRMA) has its PR work cut out for it.*

- **PORTOLA PHARMACEUTICALS' PRT-4445 – Bayer, Johnson & Johnson,** and **Portola** are all collaborating on this investigational antidote for Factor Xa inhibitors – which includes Bayer and J&J's **Xarelto** (rivaroxaban). Portola retains the global development and commercialization rights to PRT-4445. Portola already had a similar deal with **Bristol-Myers Squibb** and **Pfizer** to test PRT-4445 in their Factor Xa inhibitor, **Eliquis** (apixaban).

- **Prostate cancer –** University of Georgia researchers reported that they have identified a potential new target in prostate cancer – Pak1 (p21 activated kinase-1), which appears to be involved in tumor growth and metastasis. They are now testing whether a Pak1 inhibitor is effective in a mouse model of prostate cancer.

- **ROCKWELL MEDICAL's soluble ferric pyrophosphate (SFP) –** The company announced that this iron deficiency drug to treat patients on hemodialysis met the primary endpoint in two Phase III trials, reducing the need for erythropoiesis-stimulating agents (ESAs) by 37%. However, these were not FDA-approved trials; those are still ongoing, with results expected in 2H13.

NEWS IN BRIEF

Electronic health records (EHRs) – implementation poses challenges

- The Department of Veterans Affairs and the Department of Defense have given up (at least for now) on plans for a single, integrated EHR computer system for troops and veterans that had been planned to be ready in 2017, opting instead to use the two existing computer systems to start delivering EHRs by January 2014. But the data in both will be in a standardized format that each department can use.

- A study of healthcare CIOs found that they view EHR implementation as the No. 1 challenge and priority for 2013. More than half already have fully implemented EHRs, and 80% plan to spend more on new IT and upgrades this year than last year.

GILEAD SCIENCES' sofosbuvir (GS-7977) – positive Phase III results

The company announced top-line results from two Phase III trials in naïve hepatitis C virus (HCV) patients, and this once-daily, oral NS5B nucleotide inhibitor met the primary endpoints.

- **FISSION** tested sofosbuvir + ribavirin vs. ribavirin + pegylated interferon (PR) in HCV-2/3 patients. In the study, 67% of patients in both arms achieved sustained virologic response, but sofosbuvir patients did it in 12 weeks, and PR patients did it in 24 weeks, which met the criteria for ***non-inferiority***. Adverse events were also less frequent with sofosbuvir.

- **NEUTRINO** tested sofosbuvir + PR vs. historical control for 12 weeks in 327 HCV-1-4-5-6 patients. This study showed superiority for sofosbuvir over the historical SVR rate of 60%, with 90% of patients achieving SVR12.

Top-line results from the Phase III FUSION trial are expected in 1Q13.

IDENIX PHARMACEUTICALS' IDX-184 and IDX-19368 – giving up on these NS5B inhibitors

The company is discontinuing development of both these NS5B nucleotide polymerase inhibitors for the treatment of HCV. The FDA had put IDX-184 on partial clinical hold and IDX-19368 on full clinical hold after a patient on another NS5B inhibitor – **Bristol-Myers Squibb's BMS-986094** – suffered adverse cardiovascular events. Idenix had submitted additional cardiac safety data at the FDA's request, but the FDA declined to release the clinical hold. Idenix said it has a uridine nucleotide analog in development that is distinct from IDX-184, IDX-19368, and BMS-986094, and it expects to file an investigational new drug (IND) application in 1H13.

JOHNSON & JOHNSON and BAYER's Xarelto (rivaroxaban) – careful switching to warfarin

A new analysis of data from the ROCKET-AF trial, published in the ***Journal of the American College of Cardiology***, found that stopping Xarelto does not appear to be worse for atrial fibrillation (AFib) patients than stopping warfarin, but switching from rivaroxaban to warfarin can be problematic.

The researchers found that interruption or early permanent discontinuation of Xarelto didn't increase stroke or other thromboembolic events vs. the same changes with warfarin. However, patients who transitioned to warfarin from Xarelto after the end of the trial had more events than warfarin patients who stayed on warfarin, with 3.72-fold more strokes in the 3-30 days post-study drug in Xarelto patients.

ROCHE/GENENTECH's Avastin (bevacizumab) – Turkish counterfeits and cervical cancer

- The FDA warned that new batches of counterfeit Avastin (under the Turkish brand name, Altuzan) have shown up in the U.S. market, and at least one of these has no (zero) active ingredient in it.
- The National Cancer Institute announced that the interim analysis of a cervical cancer study found that Avastin extended median survival in some patients vs. chemotherapy alone (17 months vs. 13.3 months). Full details may be presented at ASCO 2013.

Stem cells – noteworthy studies

For the most part, stem cell therapy is too far away from commercial reality to justify inclusion in ***Quick Takes***, but two stem cell stories, both published in ***Stem Cells Translational Medicine***, caught our attention this week. Just don't think they portend any imminent use.

- **ALS.** In a 13-patient study in Mexico, researchers found that autologous CD133+ stem cells from amyotrophic lateral sclerosis (ALS) patients have the ability to develop into mature neuron-like cells, suggesting that this could be a possible new treatment option for these desperate patients.
- **Kidney transplantation.** In a 6-patient Phase I safety and feasibility study, Dutch researchers found that mesenchymal stromal cells (MSC, a kind of stem cell) may extend the survival time of a transplanted kidney.

Stroke – endovascular therapy lags in study

The SYNTHESIS Expansion trial, presented at the International Stroke Conference in Hawaii and simultaneously published in the ***New England Journal of Medicine***, found that endovascular therapy did not improve ischemic stroke outcomes any better than IV tPA given within the first 4.5 hours. The 90-day disability-free survival rate was 30.4% for endovascular patients vs. 34.8% for tPA patients. Serious adverse events were similar for the two groups.

The trial used several brands of devices – **Covidien's Solitaire, Penumbra's Penumbra System**, and **Stryker/Concentric Medical's Merci Retriever** and **Trevo**.

The Italian authors concluded: "Our findings do not provide support for the use of the more invasive and expensive endovascular therapy over intravenous treatment."

STX-MED's Cefaly – zapping migraines?

A Belgian study published in ***Neurology*** found that wearing an external TENS (transcutaneous electrical nerve stimulation) device that delivers electrical stimulation to the supraorbital nerve can cut migraine attacks. Sixty-seven people who had an average of four migraines a month were followed for one month with no treatment and then were given electrical stimulation for 20 minutes a day for three months or sham stimulation.

The patients who received stimulation had fewer migraine days in Month 3 vs. the non-treatment month (4.8 vs. 6.9), but there was no change in migraine frequency for the sham patients. The device is available in Europe, some South American and Middle Eastern countries, and Canada, but it is not yet FDA-cleared.

REGULATORY NEWS

CMS initiative to improve ESRD care

The Centers for Medicare & Medicaid Services (CMS) announced a new program – the Comprehensive ESRD Care Initiative – designed to identify, test, and evaluate ways to improve care for Medicare beneficiaries with end-stage renal disease (ESRD). The key focus is enhanced care coordination.

CMS plans to make agreements with groups of healthcare providers and suppliers – called ESRD Seamless Care Organizations. These organizations – which must include a dialysis facility, a nephrologist, and one other Medicare provider or supplier – will assume clinical and financial responsibility for a group of ESRD beneficiaries. The patients will keep the right to see any Medicare provider they choose, and the organizations will be evaluated on quality measures that include the patient's health and experience. Organizations that are successful in improving patient health outcomes and lowering the per capita cost of care will have an opportunity to share in Medicare savings with CMS.

Interested applicants must file a non-binding letter of intent by March 15, 2013, and applications are due May 1, 2013.

CMS issues physician sunshine rule

CMS issued a final rule, setting a timeline for implementation of the Physician Payments Sunshine Act. Starting August 1, 2013, drug and device companies will be required to collect data about payments, gifts, and other items of value given to physicians and teaching hospitals.

In addition, manufacturers and group purchasing organizations (GPOs) will be responsible for reporting physician ownership and investment interests, with the first round of data to be given to CMS by March 31, 2014. CMS will then post the data within six months.

CMS regulatory reforms

CMS proposed a rule that would eliminate some outdated or "overly burdensome" requirements for hospitals and healthcare professionals. Among the changes:

- A requirement that small, critical access hospitals and rural health clinics have a physician onsite once every two weeks would disappear.
- Registered dieticians would be allowed to order patient diets without the supervision or approval of a doctor.
- Trained nuclear medicine technicians in hospitals could prepare radiopharmaceuticals for nuclear medicine without a supervising physician or pharmacist present.

FDA guidance on Alzheimer's drug development

The FDA issued a nine-page draft guidance that had good and bad news for researchers.

- **On the positive side**, it would relax the rules for early-stage Alzheimer's disease (AD) trials, allowing researchers to show simply that a medication slows cognitive decline instead of the tougher bar of showing improvement in ***both*** cognitive and functional deterioration. A delay in cognitive impairment can now be the basis for accelerated approval, with a requirement to show post-approval that the effects on cognition persist over time.

  Russell Katz, MD, director of the FDA's Neurology Products Division in the Center for Drug Evaluation and Research (CDER), said, "The scientific community and the FDA believe that it is critical to identify and study patients with very early Alzheimer's disease before there is too much irreversible injury to the brain."

- **On the negative side**, the FDA still wants two co-primary endpoints – function and cognition – for dementia therapies other than early-stage trials.

  The FDA also rejected the use of imaging (e.g., PET beta-amyloid scans) or biomarkers as a primary endpoint in pivotal AD trials, saying, "No reliable evidence exists at the present time that any observed treatment effect on such a measure is reasonably likely to predict ultimate clinical benefit…Until there is widespread evidence-based agreement in the research community that an effect on a particular biomarker is reasonably likely to predict clinical benefit, we will not be in a position to consider an approval based on the use of a biomarker as a surrogate outcome measure."

Public comments will be accepted until April 7, 2013.

FDA approvals/clearances

- **CARDIVA MEDICAL's Vascade**, an extravascular closure system for femoral access percutaneous surgery, was granted premarket approval.
- **CELGENE's Pomalyst (pomalidomide)**, an oral IMiD and an orphan drug, received accelerated approval to treat patients with multiple myeloma whose disease progressed after prior therapies, including **Revlimid** (lenalidomide) and **Roche's Velcade** (bortezomib). The drug was given a boxed warning that it should not be used in pregnant women. Because of the teratogenicity, it will be available only through the Pomalyst Risk Evaluation and Mitigation Strategy (REMS) program (which is similar to that for Revlimid), which means:
  - Prescribers must enroll and agree to comply with the REMS requirement.
  - Patients must sign a Patient-Physician agreement form and comply with the REMS requirements.
  - Women who are not pregnant but can become pregnant must comply with the pregnancy testing and contraception requirements, and males must comply with contraception requirements.
  - Pharmacies must be certified with the Pomalyst REMS Program, must only dispense to patients who are authorized to receive the drug, and must comply with REMS requirements. Both lenalidomide and thalidomide have similar REMS.
- **ELITE PHARMACEUTICALS' naltrexone hydrochloride**, an opioid receptor antagonist, was approved.
- **JOHNSON & JOHNSON/ETHICON's Enseal G2 Articulating System**, a second-generation surgical sealing device, received 510(k) clearance.
- **K7's K7C Cervical Spacer**, a spinal fusion device using PEEK (polyetheretherketone), received 510(k) clearance.
- **PERRIGO's testosterone gel 1%**, a bioequivalent of **AbbVie's AndroGel 1%**, was approved to treat adult males with low/no testosterone.
- **RESONANCE HEALTH's FerriScan R2-MRI system** was approved for use as a companion diagnostic for **Novartis' Exjade** (deferasirox), a drug to reduce iron overload in patients with genetic blood disorders.
- **STANMORE IMPLANTS' Sculptor Robotic Guidance Arm** received 510(k) clearance for use in unicompartmental knee procedures. The company is expected to do a limited launch in mid-2013.
- **WARNER CHILCOTT's Delzicol (mesalamine)** was approved to treat ulcerative colitis.

FDA recalls/warnings

- **CRYOLIFE** received a warning letter for failing to sufficiently fix manufacturing issues the FDA had previously identified.
- **NOVO NORDISK** received a warning letter citing violations of current good manufacturing practice (cGMP) regulations at its Denmark plant, and the company's response to the FDA's initial findings was not acceptable. The concerns include: contamination, environmental monitoring, workers with inadequately sterilized goggles, batch variations, etc. The FDA said it ***may*** withhold approval of any new applications or supplements until these issues are resolved.

European regulatory news

- **DELCATH SYSTEMS' Chemosat** – The German government approved a reimbursement scheme for this liver chemotherapy procedure, and now hospitals in that country can negotiate coverage with insurers. The company hopes to build on this and spread use across Europe.
- **MEDTRONIC's Evera** – A next-generation line of these implantable cardioverter defibrillators received a CE Mark.
- **REGENERON PHARMACEUTICALS and SANOFI's Zaltrap (ziv-aflibercept)** was approved by the European Commission in combination with FOLFIRI chemotherapy in adults with metastatic colorectral cancer that is resistant to or has progressed after an oxaliplatin-containing regimen.
- **SANOFI and ZEALAND PHARMA's Lyxumia (lixisenatide)**, a once-daily injectable GLP-1 inhibitor, was approved by the European Medicines Agency (EMA) to treat Type 2 diabetes.

Regulatory news from other countries

Canada: **BAYER's Diane-35 (cyproterone acetate + ethinyl estradiol)** – Health Canada is investigating the safety of this acne drug, which was banned in France because of a blood clot risk and is being investigated by the EMA.

2013 FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
February 12	Discussion of issues in **communicating drug risks** to patients	FDA's Risk Communication Advisory Committee
February 14	**Guerbet's Dotarem** (gadoterate meglumine injection) for use in MRI imaging of the brain, spine, and related tissues to detect/visualize disruption of the blood brain barrier and/or abnormal vascularity (abnormal blood circulation)	FDA's Medical Imaging Drugs Advisory Committee
February 22	**NeuroPace's RNS system,** a neuromodulation system for epilepsy	FDA's Neurological Devices Advisory Committee
February 24	**Dynavax's Heplisav** hepatitis B vaccine	PDUFA date
February 26	**Roche/Genentech** and **ImmunoGen's trastuzumab emtansine** (T-DM1) to treat unresectable locally advanced or metastatic HER2+ breast cancer	PDUFA date
February 28	**Lundbeck** and **Otsuka's aripiprazole depot** to treat schizophrenia	PDUFA date
March 1	**Zogenix's Zohydro** (extended-release hydrocodone) for chronic pain	PDUFA date
March 4	**Depomed's gabapentin** and **Noven Therapeutics' paroxetine** – both to treat moderate-to-severe vasomotor symptoms of menopause	FDA's Reproductive Health Drugs Advisory Committee
March 5	Efficacy vs. cancer risk with calcitonin-salmon products **– Novartis' Miacalcin** (calcitonin-salmon – injection and nasal spray) and **Upsher-Smith Laboratories' Fortical** (calcitonin-salmon recombinant nasal spray) – for the treatment of postmenopausal osteoporosis	Joint meeting of the FDA's Reproductive Health Drugs Advisory Committee and the FDA's Drug Safety and Risk Management Advisory Committee
March 7	**GlaxoSmithKline's Breo Ellipta** (fluticasone furoate + vilanterol), a dry powder inhaler for chronic obstructive pulmonary disease (COPD)	FDA's Pulmonary-Allergy Drugs Advisory Committee
March 17	**Bristol-Myers Squibb** and **Pfizer's Eliquis** (apixaban,) an oral anticoagulant to prevent stroke in atrial fibrillation patients	PDUFA date
March 18	**Pharmaxis' Bronchitol** (mannitol) for cystic fibrosis	PDUFA date
March 28	**Biogen Idec's BG-12** (dimethyl fumarate) for multiple sclerosis	PDUFA date (extended from December 28, 2012)
March 31	**Johnson & Johnson's Invokana** (canagliflozin), a SGLT2 inhibitor to treat Type 2 diabetes	PDUFA date
April 15	**MAP Pharmaceuticals' Levadex** (dihydroergotamine), inhaled migraine drug	PDUFA date
April 29	**Shire's Vyvanse** (lisdexamfetamine dimesylate), sNDA for ADHD treatment in children	PDUFA date
April 29-30	Discussion of **medical device labeling standardization**, including an online labeling repository for in-home medical devices	FDA public workshop
April 30	**Raptor Pharmaceutical's cysteamine bitartrate** delayed-release (RP-103) to treat nephropathic cystinosis	PDUFA date (extended from January 30, 2013)
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
June 20	**Dainippon Sumitomo Pharma/Sunovion Pharmaceuticals' Latuda** (lurasidone), a schizophrenia drug for use in treating bipolar disorder	PDUFA date
July	**PET imaging** of brain beta-amyloid	CMS coverage decision expected
July 28	**Aveo Oncology** and **Astellas Pharma's Tivopath** (tivozanib) to treat advanced renal cell carcinoma	PDUFA date
October 2	**Lundbeck** and **Takeda's Brintellix** (vortioxetine), an antidepressant for major depressive disorder	PDUFA date
October 19	**Actelion's Opsumit** (macitentan), a dual endothelin receptor antagonist to treat pulmonary arterial hypertension	PDUFA date