TRENDS-in-MEDICINE

October 21, 2012

by Lynne Peterson

Quick Takes

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

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's Endocrinologic and Metabolic Drugs Advisory Committee meetings on **Aegerion Pharmaceuticals' lomitapide** and **Sanofi/Genzyme and Isis Pharmaceuticals' Kynamro (mipomersen)**, both drugs for homozygous familial hypercholesterolemia (HoFH).

SHORT TAKES

- **ABBOTT's ABT-450 –** The company announced that the 12-week, 571-patient Phase IIb AVIATOR trial (M11-652), in which ABT-450/ritonavir (QD) was combined with three other drugs – ABT-267 (QD) + ABT-333 (BID) + ribavirin – had an SVR12 of 99% in treatment-naïve hepatitis C (HCV-1) patients and 93% in prior null responders. Details will be presented at the American Association for the Study of Liver Diseases (AASLD). For Phase III, Abbott plans to test ABT-450/r + ABT-267 + ABT-333 ± ribavirin.

- **ABBOTT and REATA PHARMACEUTICALS' bardoxolone methyl –** The Phase III BEACON trial of this investigational drug for Stage 4 chronic kidney disease (CKD) was stopped after the data safety monitoring committee found "excess serious adverse events and death." The companies have not decided whether all development will be scrapped.

- **AEGERION PHARMACEUTICALS' lomitapide –** The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 13-2 to recommend approval of this oral treatment for homozygous familial hypercholesterolemia (HoFH).

- **Antidepressants –** A meta-analysis of 16 studies with ~500,000 patients – published in the journal ***Neurology*** – linked use of selective serotonin reuptake inhibitor (SSRI) antidepressants with an increased risk of a hemorrhagic stroke, but the risk is still very, very small (~1 in 10,000/year).

- **ARQULE and DAIICHI SANKYO's tivantinib –** The company reached agreement with the FDA on the terms for a special protocol assessment (SPA) for the design of a pivotal Phase III trial of this investigational MET inhibitor in ~300 patients with inoperable hepatocellular carcinoma and plans to start the trial by early 2013. The primary endpoint will be overall survival, and a key secondary endpoint will be progression-free survival.

- **Arthroplasty –** A study of >900 patients, reported in ***Diabetes Care***, found that Type 2 diabetics were more likely to need arthroplasty than non-diabetics. The rate was 17.7 per 1,000 person-years in diabetics vs. 5.3 for non-diabetics. Duration of diabetes also was associated with an increased likelihood of arthroplasty in both men and women.

- **ASTRAZENECA** plans to work with **Pharmaron**, a Chinese research company, to speed discovery of new medicines.

- **Autism** – The FDA approved a 30-patient study of autologous stem cells from umbilical cord blood to treat autism in children age 2 to 7.

- **BAXTER** put plans to buy a privately held compounding firm, **PharMEDium Healthcare**, on hold until the full fallout from the meningitis outbreak – along with any regulatory and/or legislative changes – becomes clear.

- **BIOCRYST PHARMACEUTICALS** is buying **Presidio Pharmaceuticals**, and the merged companies will focus on antiviral and orphan drugs. Presidio's lead drug is PPI-668, an oral, once-daily, pan-genotypic NS5A inhibitor to treat hepatitis C (HCV). BioCryst's portfolio includes BCX-5191, an NS5B nucleoside analog to treat HCV, as well as BCX-4161, a plasma kallikrein inhibitor to treat hereditary angioedema (HAE), and other agents.

- **BIOGEN IDEC's BG-12 (dimethyl fumarate)** – The FDA extended its review of this investigational oral drug to treat multiple sclerosis by three months, moving the PDUFA date from December 28, 2012, to March 28, 2013.

- **Compounding pharmacies** – Methylprednisolone acetate and two other drugs compounded by the **New England Compounding Center (NECC)** – the steroid triamcinolone acetonide and a cardioplegic solution used during open-heart and heart transplant surgery – have been linked to patient infections (with *aspergillus* fungi and *exserohilum* fungi). So far, 284 infections and 23 deaths have been reported, and the numbers continue to climb.

- **EHEALTH TECHNOLOGIES**, which provides imaging solutions for electronic health records (EHR) and health information exchange (HIE) solutions, has partnered with **InterSystems** to provide single-click, instant access to diagnostic-quality images (x-ray, CT, MRI, and ultrasound) via the InterSystems HealthShare informatics platform.

- **EISAI's Zonegran (zonisamide)** – A study funded by the National Institutes of Health and published in the ***Archives of Internal Medicine*** suggested that this epilepsy drug may help obese adults lose weight when combined with routine nutritional counseling. On average, patients lost ~7.5 more pounds on 400 mg Zonegran than with diet/lifestyle alone, but they also had more adverse events.

- **EPIOMED THERAPEUTICS** – NASA is working with Epiomed to develop a scopolamine nasal spray to treat motion sickness quickly. NASA wants this for astronauts, but Epiomed could commercialize it, too.

- **GILEAD SCIENCES' Viread (tenofovir)** – A study presented at the American Association of Pharmaceutical Scientists meeting found that a vaginal ring could deliver appropriate levels of tenofovir for HIV prevention – at least in sheep.

- **HORIZON DISCOVERY**, which provides research tools for the development of personalized medicines, established a Center of Excellence for rAAV-mediated genome editing with Washington University in St Louis and the BRIGHT Institute to translate human cell lines, developed at Washington University and licensed to Horizon, using Horizon's Genesis technology to alter specific genes involved in the development and progression of cancer.

- **Implantable cardioverter defibrillators (ICDs)** – An 81-patient study published in the ***Annals of Internal Medicine*** found that ICDs explanted from U.S. patients can be safely reused in patients in India after resterilization. The researchers found no evidence of infection or malfunction with the recycled ICDs. Recycling is prohibited by the FDA because they are single-use devices, but this could be a way to make devices available for patients in other countries.

- **KAMADA's AATD-IH** – The FDA gave the go-ahead to a Phase II/III trial of this inhaled treatment for congenital emphysema due to a deficiency of the alpha-1 antitrypsin protein.

- **LEXICON PHARMACEUTICALS' telotristat etiprate** – The company said a Phase II study of this drug – an experimental medication for carcinoid syndrome that was granted both fast track and orphan drug status by the FDA – met the primary endpoint, reducing bowel movements in patients with gastrointestinal cancer. Lexicon said that 75% of patients reported improvement in symptoms by Week 12. A Phase III trial is underway.

- **LILLY/IMCLONE's ramucirumab** – The company said a Phase III trial found that this investigational VEGFR-2 inhibitor prolonged survival in metastatic gastric cancer patients but didn't say how much longer the patients lived.

- **MERCK's odanacatib** – The company said a 243-patient study of this once-weekly oral cathepsin K inhibitor improved bone mineral density in osteoporotic women.

- **NPS PHARMACEUTICALS' Gattex (teduglutide)** – The FDA's Gastrointestinal Drugs Advisory Committee voted unanimously (12-0) to recommend approval of this investigational treatment for short bowel syndrome (SBS) as an orphan drug. While the drug is associated with gastrointestinal obstruction, pancreatic disorders, and accelerated colon polyp development, the panel was relatively

comfortable with the drug's safey profile, though it recommended that more safety data be collected postmarketing.

- **NOVARTIS' Sandostatin (octreotide)** – In an 86-patient Phase III trial in malignant bowel obstruction – presented at the International Congress on Palliative Care – Sandostatin "was no better than standard drugs in controlling vomiting."

- **NOVAVAX's avian flu vaccine** – The company announced positive results from two Phase I trials of this H5N1 vaccine and plans to continue development.

- **NOVO NORDISK's turoctocog alfa (NN-7008)**, an investigational treatment for hemophilia A, was submitted to both the FDA and the European Medicines Agency (EMA).

- **PFIZER/AGOURON's Viracept (nelfinavir)** – This aspartyl protease inhibitor for HIV may have a new use – inhibiting the growth of HER2-positive breast cancer cells. A study published in the ***Journal of the National Cancer Institute*** reported that both *in vitro* and *in vivo* testing found that nelfinavir selectively inhibits growth of HER2+ breast cancer cells even in cell lines with proven resistance to **Roche's Herceptin** (trastuzumab) and/or **GlaxoSmith-Kline's Tykerb** (lapatinib).

- **ROCHE's Actemra (tocilizumab)** was granted an expanded indication to treat adults with moderate-to-severe rheumatoid arthritis (RA) who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (e.g., TNF-inhibitors), making it a second-line therapy.

- **SANOFI/GENZYME and ISIS PHARMACEUTICALS' Kynamro (mipomersen)** – The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 9-6 to recommend approval of this injectable therapy for HoFH.

- **ST. JUDE MEDICAL**'s plant in Sylmar CA (where the Riata leads were made) is being audited by the FDA, and the company's CEO said the investigation may result in a warning letter, though he didn't explain why.

- **TRINITY HEALTH and CATHOLIC HEALTH EAST** are consolidating their operations, which include 82 hospitals in 21 states. The two networks do not overlap; their hospitals are in different locations. The combined operation also includes 89 continuing-care facilities and >87,000 employees.

NEWS IN BRIEF

European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)

- **Biogen Idec's daclizumab.** The Phase II SELECTION extension trial of this anti-IL-2 antibody showed efficacy was maintained in the second year, but serious autoimmune side effects also were reported, with one patient dying from autoimmune hepatitis and two others developing autoimmune conditions affecting vital organs.

- **Biogen Idec's BG-12 (dimethyl fumarate).** The company said that a closer look at data from two Phase III trials (DEFINE and CONFIRM) confirmed previous findings that oral BG-12 significantly reduces relapses and progression of disability.

- **Novartis' secukinumab (AIN-457).** A 73-patient, six-month, placebo-controlled, proof-of-concept study in Eastern Europe found that this anti-IL-17a significantly lowered T1 and T2 brain lesions, with a trend toward a relapse rate reduction. The side effect to watch is infections.

- **Sanofi's Lemtrada (alemtuzumab).** Sanofi said it has a next-generation version of Lemtrada ready to start Phase I.

Hip resurfacing – fails in U.K. study

A U.K. study published in ***The Lancet*** found that hip resurfacing was not as effective as total hip replacement for male patients with smaller femoral heads (<54 mm), with worse implant survival. Implant survival was comparable for larger femoral heads.

Using data from the National Joint Registry for England and Wales, the researchers analyzed 434,560 primary total hip replacements from 2003 through 2011, and 7.3% of these were resurfacings. The 5-year revision rate for resurfacing was 5.2% vs. 2.8% for stemmed total hip replacements and 8.5% for women vs. 3.6% for men. The researchers recommended that resurfacing not be undertaken in women and that preoperative measurement be used to assess suitability in men.

PFIZER

- **Inlyta (axitinib).** This VEGFR inhibitor failed to significantly improve progression-free survival (PFS) in a Phase III trial in naïve renal cell carcinoma patients, but the "miss" was narrow, and the company is studying the results to see if there are subgroups that may benefit.

- **Zyvox (linezolid).** A study published in the ***New England Journal of Medicine*** found that a 600 mg dose of this antibiotic may be effective in treating extensively drug-resistant tuberculosis, but with a high rate of adverse events.

VIVUS' Qsymia (phentermine + topiramate)

- **In the U.S.**, where this diet drug is approved, the company submitted an amendment to its Risk Evaluation and Mitigation Strategy (REMS), asking the FDA to allow it to sell Qsymia (formerly known as Qnexa) through "a broader range" of pharmacies.
- **In Europe**, any approval is now unlikely. The EMA's Committee for Medicinal Products for Human Use (CHMP) recommended against approval, citing possible safety issues with long-term use, concerns over birth defects and cardiac risks, and potential off-label use.

REGULATORY NEWS

NIH creates database of drugs that cause liver damage

The National Institutes of Health (NIH) launched a database of drugs associated with liver damage, called LiverTox, that is free for healthcare researchers and doctors. It has information on >700 drugs, with another 300 to be added in the future. Jay Hoofnagle, MD, lead creator of the new database and director of the Liver Disease Research Branch at NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), said, "Because drug-induced liver disease is not a single, common disease, it is very difficult to diagnose, with each drug causing a somewhat different pattern of liver damage."

FDA approvals/clearances

- **EDWARDS LIFESCIENCES' Sapien** – The FDA approved an expanded indication for this transcatheter aortic valve to include patients with aortic valve stenosis who are eligible for surgery but who are at high risk for serious surgical complications or death. Both the transfemoral (TF) and transapical (TA) approaches were approved.
- **HOLOGIC's Aptima HPV 16 18/45 Genotype Assay**, which is used with the firm's TIGRIS instrument system to identify the presence of human papillomavirus types 16, 18, and/or 45 in women who have tested positive for the virus, was cleared for use, and the company plans to start marketing it in early 2013.
- **INSIGHTRA MEDICAL's Freedom**, a device for treating inguinal hernia, was cleared for use.
- **LILLY's Alimta (pemetrexed)** was granted an expanded indication to include maintenance therapy in combination with cisplatin for non-squamous non-small cell lung cancer (NSCLC).
- **LOMA VISTA MEDICAL's TRUE Dilatation balloon valvuloplasty catheter** received FDA clearance.
- **PARADIGM SPINE's coflex system**, which is used to treat spinal stenosis, received premarket approval.
- **ROCHE's Accu-Chek Inform II system**, a hospital blood glucose monitor, was cleared for use.
- **THROMBOGENICS' Jetrea (ocriplasmin)** was approved to treat symptomatic vitreomacular adhesion (VMA).
- **VUCOMP's Version 2 M-Vu technology**, a new version of its computer-aided device that helps radiologists detect breast cancer early, received premarket approval as an ancillary tool to digital mammography.

FDA recalls/warnings

- **ACU-INTERNATIONAL SUPPLIES' Electro Meridian Imaging device** – The company received a warning letter that this device, which the company is marketing, requires FDA clearance/approval and does not have it.
- **CELLTEX THERAPEUTICS** received a warning letter, giving it 15 business days to submit a plan to address the FDA's concerns that it is illegally marketing an unlicensed drug (a stem cell product) and has manufacturing deficiencies.
- **VENTLAB's manual resuscitators** were recalled due to a potential to deliver little to no air/oxygen through the patient valve to the patient, which could be life-threatening.

European regulatory news

- **European Union Health Commissioner John Dalli** resigned amid fraud allegations relating to tobacco policy, not drugs. A tobacco producer, Swedish Match, complained that a Maltese entrepreneur approached the company wanting money in return for a promise that he could influence future tobacco legislation through Dalli.
- **ASTUTE MEDICAL's NephroCheck**, a cartridge-based immunoassay test to predict the risk of acute kidney injury, received a CE Mark.
- **European Diagnostic Clusters Alliance** – This newly formed group is a public/private collaboration, based in Belgium, aimed at aiding *in vitro* diagnostics startups in

Europe by facilitating partnerships and networking and by helping firms obtain easier access to the U.S., Asia, and other markets outside the region.

- ONCOSEC's **OncoSec Medical System**, an electroporation device (which opens pores in targeted tumor membranes during immunotherapy and chemotherapy for skin cancer), received a CE Mark.

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

NICE made a major change to its procedures and will review the cost-effectiveness of drugs before they are released. These new "evidence summaries: new medicines" will include "quality-assured summaries" of the best available evidence for selected new medications as well as some existing drugs with new indications or a new formulation.

NICE said these reviews will not be used as formal guidance but to help the National Health Service (NHS) make informed decisions. A list of drugs to undergo the initial reviews was released and includes:

- **Abbott's Humira (adalimumab)** for the treatment of moderate-to-severe ulcerative colitis.
- **Almirall's Eklira Genuair (aclidinium)** as maintenance treatment for chronic obstructive pulmonary disease (COPD).
- **Eisai's Fycompa (perampanel)** as an adjunctive treatment for partial-onset seizures.
- **Generic glycopyrronium** as a maintenance bronchodilator treatment for COPD.
- **Novo Nordisk's insulin degludec** for diabetes.
- **Roche's Herceptin (trastuzumab)** as a subcutaneous neoadjuvant treatment for early breast cancer and metastatic breast cancer.
- **Sanofi's Lyxumia (lixisenatide)** for Type II diabetes.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	2012	
October 23-24	**Update on scientific initiatives and accomplishments** over the past year, including an update from the NanoCore Subcommittee and from the Office of Science Coordination. In addition, CBER, CDER, and other FDA centers will discuss their center-specific research strategic needs	Science Advisory Board to the National Center for Toxicological Research meeting
October 24	**Hologic's Selenia Dimensions 3D System –** expanded indication to combine digital breast tomosynthesis with 2D images for cancer screening	FDA's Radiological Devices Advisory Committee
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 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