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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NOTE: Subscribe to ***Trends-in-Medicine*** for coverage of the **American Neurological Association** meeting in Boston.

SHORT TAKES

- **ABLYNX's ALX-0061 –** The company said a Phase I/II study of this nanobody that binds to IL-6R, which is being developed in collaboration with **Merck**, was positive in moderate-to-severe rheumatoid arthritis, meeting the primary efficacy with significant improvements in DAS28 and ACR20.

- **ANACOR PHARMACEUTICALS' GSK-2251052 – GlaxoSmithKline**, which had licensed this experimental antibiotic to treat urinary tract and intra-abdominal infections, halted development after identifying microorganisms that could adversely impact the efficacy of the drug and is returning all rights to Anacor.

- **APERTUS PHARMACEUTICALS –** The Drug Enforcement Administration (DEA) gave the company permission to manufacture several pain medications – fentanyl, sufentanil, remifentanil, and alfentanil.

- **ARDELYX's RDX-5791 – AstraZeneca** licensed the rights to this investigational NHE3 inhibitor, which is being studied for both (a) management of fluid overload in kidney (end-stage renal disease and chronic kidney disease) and heart failure patients, and (b) treatment of irritable bowel syndrome with constipation (IBS-C).

- **BOSTON SCIENTIFIC** is buying **Rhythmia Medical**, a developer of cardiac mapping and navigation software for use in cardiac catheter ablations.

- **CAREFUSION** is buying **Intermed Equipamento Medico Hospitalar**, a respiratory device company in Brazil.

- **COAXIA's NeuroFlo catheter**, which is used to treat patients with cerebral ischemia, will be reviewed by the FDA's Neurological Devices Advisory Committee on November 1, 2012. The device, which already has a CE Mark, was granted a humanitarian device exemption (HDE) by the FDA in 2005. The FDA noted that NeuroFlo "is identical in design to the CoAxia FloControl," which is cleared for use in the peripheral vasculature.

- **Drug adverse events –** Scientists at the University of Virginia and at West Virginia University have developed a mathematical formula for computers that searches through online data – from websites, online news articles, patient communications, online chatrooms, social media, etc. – to find reports of serious adverse drug reactions. The program then organizes the adverse event by seriousness.

- **ENDO PHARMACEUTICALS' Opana ER (oxymorphone hydrochloride extended-release)** – The FDA issued a warning that abusing this oral painkiller by injecting it into the bloodstream can cause thrombotic thrombocytopenic purpura, a potentially fatal blood disorder.

- **INOVIO PHARMACEUTICALS' VGX-3100** – An 18-patient Phase I study published in ***Science Translational Medicine*** found that this investigational DNA vaccine provoked a strong immune response against precancerous cervical cells. All of the women had already been treated with standard therapies for precancerous conditions associated with infection with HPV-16 and HPV-18.

- **MERCK's Zocor (simvastatin)** – A 140-patient study presented at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Lyon, France, found that 80 mg/day simvastatin had an annualized rate of brain volume loss of 0.298% vs. 0.589% for placebo (p=0.003). In addition, simvastatin significantly reduced disability by EDSS and by MS Impact Score (MSIS).

- **PFIZER's ALO-02 (oxycodone + naltrexone)** – The company said a 395-patient Phase III trial of this investigational pain medication with a tamper-resistant formulation found that the long-term safety profile was similar to comparable medications. However, ~60% of patients dropped out, with 19% due to adverse events.

- **Pneumonia vaccines** – The Centers for Disease Control and Prevention (CDC) is recommending that adults with a compromised immune system get vaccinated with both **Pfizer's Prevnar 13** and **Merck's Pneumovax 23**.

- **REPROS THERAPEUTICS' Proellex (telapristone acetate)** – The FDA partially lifted the clinical hold on this oral investigational drug to treat endometriosis and uterine fibroids, allowing the company to initiate a Phase II trial of a low dose. The company hopes the results of that trial will allow the partial hold to be lifted.

- **ROCHE/GENENTECH's Lucentis (ranibizumab)** – A 1,126-patient trial reported in the journal **Ophthalmology** found that this anti-VEGF therapy can preserve and even improve the driving ability of patients with age-related macular degeneration (AMD).

- **ST. JUDE MEDICAL's Riata defibrillator leads** – ***The Wall Street Journal*** reported that the company may have known about the lead fracture problem as early as 2005 but characterized the problem as "isolated."

- **TAKEDA** is buying **LigoCyte Pharmaceuticals**, which is developing a vaccine to prevent norovirus.

- **VAXXAS' Nanopatch** – **Merck** is working with this Australian company to develop a skin-patch delivery system for vaccines. Human clinical trials are not expected to start for another two years.

- **VIIV HEALTHCARE and SHIONOGI's dolutegravir** – The companies said they have the results of the two Phase III trials in treatment-experienced patients – VIKING-3 and SAILING – that will be used along with the Phase III SPRING-2 and SINGLE trials in treatment-naïve patients in support of worldwide regulatory filings later this year for this HIV drug.

- **WATSON PHARMACEUTICALS** won European Union approval of its planned purchase of **Actavis Group**, another generic drug manufacturer.

NEWS IN BRIEF

Alzheimer's disease – prevention trial drugs chosen

Two anti-beta-amyloid agents – **Lilly's solanezumab** and **Roche/Genentech's gantenerumab** – along with **Lilly's LY-2886721**, a beta secretase inhibitor, were chosen for the DIAN-TU (Dominantly Inherited Alzheimer's Network Trials Unit) prevention trial in people with young-onset ***genetic*** Alzheimer's. The 160-patient trial will enroll patients in the U.S., Australia, and the U.K. and will study changes in the brain that precede the development of symptoms.

The Alzheimer's Association is the lead funder of the project (56%), with a consortium of 10 pharmaceutical companies providing the rest of the funding. The proposed trial design has two stages: (1) to determine the biological target for the drug and (2) to determine if there is a cognitive benefit to the drug. The trial is expected to start by early 2013. The principal investigator will be Randall Bateman, MD, a neurologist from Washington University School of Medicine.

Centers of Excellence – preferred sites for employers

Starting in January 2013, Walmart employees and their dependents enrolled in the company's health plan will be able to go to any of six Centers of Excellence – Mayo Clinic, Cleveland Clinic, Geisinger Medical Center, Scott & White Healthcare in Texas, Mercy Hospital Springfield in Missouri, and Virginia Mason Medical Center in Seattle – for cardiac, spine, and transplant surgery – at no cost (no out-of-pocket expense), and this includes travel expenses. And Walmart is not the only large employer that has found a win-win in offering patients expanded access to Centers of Excellence. Increasingly, employers are finding that patients get top-tier care but at a more affordable cost from these sites.

Meningitis outbreak – affecting more than patients

The number of patients developing fungal meningitis continues to grow – with at least 201 people affected, including 15 deaths – from injections of a contaminated compounded steroid (methylprednisolone acetate), and it is no longer just patients who got epidural injections for pain. There are also reports of patients developing septic arthritis from joint injections.

The outbreak also is starting to have much broader implications than just the patients who got the injections. For instance:

- **Ameridose**, a compounding pharmacy, and **Alaunus Pharmaceutical**, a distribution center, voluntarily halted their compounding production and distribution pending an inspection by the Massachusetts Department of Health even though none of their products has been shown to be contaminated. This is the second compounding pharmacy to cease operations (including distribution of all products) as a result of the outbreak.
- Congress is investigating, so this issue will stay in the news. And legislation to give the FDA (or other regulatory bodies) more authority to oversee compounding pharmacies is likely. In addition, Sen. Richard Blumenthal (D-CT) asked the Department of Justice to conduct a criminal investigation into potential fraud violations by the New England Compounding Center at the heart of the outbreak.
- The FDA looks bad whether or not it had the authority to do more to prevent this outbreak, and that is likely to increase the FDA's safety consciousness even beyond compounding pharmacies. What form that will take is still to be seen, but it could make scrutiny of unrelated areas tougher, such as oversight of drug company manufacturing plants, clinical trial sites, and drug trial safety data.

There are still ~7,500 compounding pharmacies in the U.S., but compounded drugs could become harder to get or doctors could become less willing to order them. *Will **Roche/Genentech's Avastin** (bevacizumab) for wet age-related macular degeneration be one of these?*

Multiple sclerosis
– CCSVI doesn't work but patients still getting it

Doctors have been continuing to perform chronic cerebrospinal venous insufficiency (CCSVI) procedures – a controversial treatment for multiple sclerosis in which angioplasty or stents are used to open narrow or twisted veins in the neck and chest to drain blood from the brain – despite an FDA warning that there is no clear evidence CCSVI exists in MS patients and that it has not been shown to be safe or effective. It is a practice of medicine issue, so the FDA can issue warnings but not forbid it.

In the latest trial – the 1,874-patient Italian CoSMo study, reported at ECTRIMS – ultrasound examinations found only 3.26% of MS patients had a venous obstruction vs. 2.13% of healthy controls. The researchers concluded, "CCSVI is not a disease connected to multiple sclerosis," and the Italian Multiple Sclerosis Society declared the theory dead. *Maybe these data will convince U.S. doctors and patients to stop doing these procedures.*

New drug safety
– high rate of later problems with new drugs

A Canadian study reported in a research letter in the ***Archives of Internal Medicine*** looked at the 434 new molecular entities approved in Canada between 1995 and 2010 to see how many later developed a serious safety issue. The study found:

- 34% of drugs approved under priority review developed a safety issue vs. 20% for drugs with a standard review.
- 24% of these drugs developed a later safety issue.
- 36% of priority review drugs that were not major therapeutic advances developed a serious safety issue vs. 20% of standard review drugs that were not major therapeutic advances.

In an accompanying commentary, Thomas Moore of the Institute for Safe Medication Practices suggested copying the U.K.'s practice of putting a "special warning akin to the black triangle" on new drugs for the first three years post-approval.

NONO's NA-1
– positive Phase II data in ischemic stroke

A double-blind, randomized, proof-of-concept, 185-patient, Phase II ENACT study published in ***The Lancet Neurology*** found that this investigational IV agent, a cell-permeant eicosapeptide, reduced the number of new ischemic strokes seen on MRI 12 to 96 hours after endovascular repair of an intracranial aneurysm when administered at the end of the procedure (4.1 vs. 7.3 with placebo).

However, the drug was not associated with lower stroke volumes. The researchers suggested the findings provide evidence that the drug is neuroprotective but said the findings need to be confirmed in a larger trial. In an accompanying editorial, the commentator said the findings – along with data on a Chinese drug (ginsenoside-Rd) and endaravone – may

counter some of the pessimism about developing a neuro-protectant.

VA use of Type 2 diabetes drugs – very variable despite formularies

A study by researchers at the Department of Veterans Affairs, published in the ***Archives of Internal Medicine***, found that use of expensive Type 2 diabetes drugs varies widely at the 139 VA clinics, despite national formularies. The researchers looked at data on nearly a million VA patients who received ~6.2 million prescriptions for Type 2 diabetes drugs in 2009. The researchers said that adjusting for patient characteristics "explained virtually none of the facility-level variation."

VA Use of Type 2 Diabetes Drugs

Measurement	Range	Median use
TZDs – GlaxoSmithKline's Avandia (rosiglitazone) and **Takeda's Actos** (pioglitazone)	1.4% - 25.4%	8.2%
Long-acting insulins – Sanofi's Lantus (insulin glargine) and **Novo Nordisk's Levemir** (insulin detemir)	4% - 71.2%	40.6%

REGULATORY NEWS

FDA considers speedier approval plans

FDA Commissioner Margaret Hamburg, MD, said the FDA may conduct speedier approvals of "drugs deemed to offer societal benefit despite their risks." The FDA is considering allowing pharmas to use an accelerated pathway for infectious disease treatments, antibiotics to combat drug-resistant bacteria, and weight-loss drugs for obesity. This could mean faster clinical trials with a smaller number of patients than currently required. Dr. Hamburg also suggested that a "special medical use" label might be used that would enable physicians to prescribe the drugs for patients with the most dire need.

FDA approvals/clearances

- **BAXANO's iO-Tome**, which aids in the removal of the facet joint during spinal fusion surgery, was cleared for use.
- **CELGENE's Abraxane (nab-paclitaxel)** was approved for a new indication – first-line treatment of non-small cell lung cancer in combination with carboplatin in patients not able to undergo surgery or radiation.
- **DEXCOM's G4 Platinum** continuous glucose monitoring system was cleared for use.
- **INTEGRA LIFESCIENCES' Integra Vu aPOD Prime Intervertebral Body Fusion Device** was given expanded approval to include anterior lumbar interbody fusion surgery.
- **MISSION PHARMACAL's Binosto (alendronate sodium)**, a once-weekly osteoporosis treatment, was approved.
- **QUEST DIAGNOSTICS/FOCUS DIAGNOSTICS' Simplexa Flu A/B & RSV Direct assay**, which is used in conjunction with the **3M Integrated Cycler** to help detect and distinguish the RNA of respiratory syncytial virus as well as influenza A and B viruses, received 510(k) clearance.
- **RESPIRATORY MOTION's ExSpiron**, which uses a monitor linked to an electrode pad to measure air flow in a non-ventilated patient's lungs, received 510(k) clearance.
- **SUREFIRE MEDICAL's angiographic catheters**, for use by interventional radiologists performing infusion procedures, received 510(k) clearance.
- **TRIVASCULAR's Ovation system** for treating abdominal aortic dissections received premarket approval.
- **VOLCANO's Visions PV 0.35**, the latest version of its intravascular ultrasound catheter for digital imaging of large vessels, received 510(k) clearance.

FDA recalls/warning letters

- **AKORN's pilocarpine hydrochloride ophthalmic solution** – The FDA sent a warning letter telling the company to stop manufacturing this *unapproved* prescription drug.
- **ANALYTICON BIOTECHNOLOGIES' CombiScreen Urine Test Strips** – The FDA sent a warning letter to this German firm saying that it has not fixed quality control issues at its plant, that it did not submit a new 510(k) application for modifications to its test strips, and that it may be illegally marketing the strips.
- **BAUSCH + LOMB's pilocarpine hydrochloride ophthalmic solution** – The FDA sent a warning letter telling the company to stop manufacturing this *unapproved* prescription drug.
- **FIRST MEDICAL SOURCE's pain management kits** – The company got a second warning letter from the FDA saying that it still has not documented or conducted design validation tests for its pain management kits and that it has not shown proof that it corrected a leakage problem.

- **HOSPIRA's Symbiq, Plum, Gemstar, and Lifecare PCA branded infusion pumps and IV sets –** The FDA sent a warning letter saying that these products, made in the company's Costa Rica plant, have quality problems and the company has not taken adequate action to fix the problems, which include inaudible alarms and unrestricted free-flow conditions.
- **ISOAID's Advantage Iodine-125 and Advantage PD-103 brachytherapy seeds plus the Advantage-Strand/Advantage-Load brachytherapy kit –** The FDA sent *another* warning letter to the company regarding defects in its sterilization process and lack of validation for its heat sealer process.
- **SANOFI PASTEUR's Typhim Vi –** The company recalled 16 batches of this typhoid vaccine over concerns about effectiveness. The U.K's Medicines and Healthcare products Regulatory Agency (MHRA) said the issue is not safety but reduced potency – that the vaccine "may not be as effective as it should be." The MHRA said more than 700,000 people could have received weak vaccine. Sanofi Pasteur said it has determined the cause of the problem, but a shortage will exist for a few months
- **ZIMMER's Trilogy Acetabular Cup products and Trilogy Spike Cup products –** The company received an FDA warning letter after an inspection of its Puerto Rico factory where these artificial hips are made found flaws in the manufacturing and testing process

European regulatory news

- **HYGIEIA's d-Nav Diabetes Insulin Guidance System** received a CE Mark.
- **VOLCANO's Visions PV 0.35**, the latest version of its intra-vascular ultrasound catheter for digital imaging of large vessels, received a CE Mark.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	2012	
October 16	**NPS Pharmaceuticals' Gattex** (teduglutide) for short bowel syndrome	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 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 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 28	**Biogen Idec's BG-12** for multiple sclerosis	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 disease	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
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
July 28	**Aveo Oncology** and **Astellas Pharma's tivozanib** to treat advanced renal cell carcinoma	PDUFA date