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 Congress of Obstetricians and Gynecologists (ACOG)** meeting in New Orleans and the **American Urological Association (AUA)** meeting in San Diego.

SHORT TAKES

- **ABBVIE**'s all-oral direct-acting antiviral (DAA) combination – ABT-450/ritonavir + ABT-267 + ABT-333 with and without ribavirin – was granted Breakthrough Therapy designation by the FDA to treat hepatitis C virus (HCV) in genotype 1 patients.

- **CUBIST PHARMACEUTICALS' CXA-201 (ceftolozane + tazobactam) –** The FDA granted fast track status to this investigational antibiotic for both hospital-acquired bacterial pneumonia and complicated urinary tract infections. It already had fast track status for complicated intra-abdominal infections.

- **ENDO HEALTH SOLUTIONS' Opana ER (oxymorphone extended-release) –** The FDA rejected a tamper-resistant claim for the reformulated version of Opana ER, which replaced the original version, which means that generics of the old formulation – right now just one from **Impax Laboratories** – can remain on the market. The FDA did not agree that the abuse-deterrent technology in new Opana has shown less abuse potential since its approval. In fact, the FDA criticized the new Opana, saying it may actually be more abused via injection than the original version.

- **IMPETO MEDICAL's Sudoscan –** A study presented at the American Association of Clinical Endocrinologists meeting found that diabetics with neuropathy had worse electrochemical skin conductance on Sudoscan vs. diabetics without neuropathy. The researcher suggested the test may be useful for early diagnosis of diabetic neuropathy and for evaluation of responses to therapeutic interventions.

- **INX MEDICAL** submitted an application to the FDA for its so-far-unnamed device designed to assist surgeons during hemorrhoid removal procedures.

- **NOVO NORDISK's Tresiba (insulin degludec) –** In a study presented at the American Association of Clinical Endocrinologists annual meeting, degludec beat **Sanofi's Lantus** (insulin glargine) in reducing nocturnal hypoglycemia in Type 1 diabetics.

- **NUVASIVE** brought much of its implant manufacturing in-house with the purchase of **ANC**, an Ohio spine implant manufacturer that was one of NuVasive's implant suppliers. The new facilities will be called **NuVasive Manufacturing**, LLC.

- **Somatostatin analogs –** Radiolabeled somatostatin analogs, normally used to treat cancer, may have a new use – helping target inflammation in cardiovascular disease (CVD). An 11-patient, retrospective study presented at the International Conference on Nuclear Cardiology and Cardiac CT in Berlin found that peptide receptor radionuclide

therapy (PRRT) with radiolabeled somatostatin analogs might be a useful therapeutic approach to decrease levels of inflammation in the atherosclerotic plaques of patients with cardiovascular disease.

NEWS IN BRIEF

Arteriovenous malformations (AVMs) – medical management beats intervention

Enrollment in the ARUBA trial was stopped early after a pre-planned interim analysis of 224 patients at 33 months suggested that medical therapy for AVMs in the brain was clearly superior to invasive treatment with endovascular interventions, radiation treatment, or open surgery, either alone or in combination. Patients already enrolled will continue to be followed.

The study, sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), found that the event rate (including all-cause death and hemorrhagic or ischemic stroke) in the intervention group was more than three times higher than in the medical management group.

Detailed results are expected to be presented at the European Stroke Conference in London later this month.

BAXTER's Gammagard (intravenous gammaglobulin, IVIG) – doesn't work in AD

A Phase III trial failed to show any reduction in cognitive decline or preservation of functional abilities in mild-to-moderate Alzheimer's disease patients. However, in the randomized, double-blind, placebo-controlled, multicenter (U.S. and Canada), 18-month, 390-patient Gammaglobulin Alzheimer's Partnership Study, the high dose (400 mg/kg) showed a trend to a positive change in cognition in patients with moderate disease and in patients with the apolipoprotein E4 genetic marker. Baxter said it is reconsidering its current approach to its Alzheimer's program and will determine next steps after full data analyses. *Watch for the data at the Alzheimer's Association International Conference in Boston in July 2013.*

BOSTON SCIENTIFIC's Watchman – positive longer-term data

Long-term (4-year) mortality data from the pivotal PROTECT-AF trial with this left atrial appendage (LAA) closure device for stroke prevention in atrial fibrillation patients were presented at the Heart Rhythm Society (HRS) meeting, showing that Watchman was statistically superior to warfarin in terms of all-cause mortality (3.2% vs. 4.8%) and cardiovascular mortality (1.0% vs. 2.4%).

In the initial publication of the trial, there was a higher number of adverse events with Watchman vs. warfarin, but with the longer follow-up that difference was no longer significant. However, 22 Watchman patients had pericardial tamponade requiring extended hospitalization. Adverse events went down as doctors gained more experience with the device.

Breast cancer – predicting outcomes in DCIS

A study published in the ***Journal of the National Cancer Institute*** found that the ductal carcinoma *in situ* (DCIS) Score quantifies the risk of an ipsilateral breast event (IBE) and invasive IBE risk, complementing both traditional clinical and pathologic factors and helping to provide another tool to improve the process of selecting individualized treatment for women with DCIS who meet the criteria.

In an accompanying editorial, Christine Berg, MD, called the assay a step forward but cautioned that there were limitations to the study. For instance, it was done in a selected subset of patients, so the clinical applicability of this assay for all women who present with DCIS "remains to be determined."

CELSUS THERAPEUTICS' MRX-6 – positive results in dermatitis

The company announced positive Phase II results from the 30 patients in the 2% dose cohort in allergic contact dermatitis, with a statistically significant 56% improvement in symptoms (PVA score) vs. 24% for control ($p<0.0001$) with this investigational, non-steroidal, multi-functional anti-inflammatory drug (MFAID), an sPLA2 inhibitor.

Change in Symptoms with MRX-6 Phase II Trial

Measurement	MRX-6	Control	p-value
PVA	–56%	–24%	<0.0001
Scaling	–45%	–22%	0.0130
Redness	–47%	–20%	0.0006
Pruritus	–63%	–28%	0.0059
Fissures	–79%	–44%	0.0045
Dryness	–46%	–15%	0.0008

Insulin – PCPs hesitant to start insulin

A study reported at the American Association of Clinical Endocrinologists meeting found that a survey of primary care physicians (PCPs) at a Pennsylvania hospital found:

- 97% said their patients would be willing to start insulin if needles weren't required.

- 66% said they delayed initiation of insulin therapy for Type 2 diabetics because of concerns that their patients would find it too much of a burden.
- 69% said going on insulin would be viewed by patients as a failure to manage their disease.
- 53% said the different types of insulin products created confusion in prescribing.
- ~60% thought that insulin regimens were too complicated for most patients to understand.
- 16% deemed insulin therapy too expensive.
- 38% said insulin therapy was too time-consuming.

Omega-3 fatty acids – no benefit in AMD

The randomized, 1,608-patient AREDS study published in ***JAMA*** found that adding lutein, zeaxanthin, or omega-3 fatty acids to vitamin supplements that are used to help prevent the progression of age-related macular degeneration (AMD) does not improve outcomes. Emily Chew, MD, PhD, an ophthalmologist and deputy director of the Division of Epidemiology and Clinical Applications at the National Eye Institute, said, "We can clearly say the omega-3s didn't add anything."

Oncology trials – not as robust as other trials

Duke University researchers reported an analysis, published in ***JAMA Internal Medicine***, of ~9,000 oncology drug trials conducted between 2007 and 2010. The analysis was part of the Clinical Trials Transformation Initiative, a public-private partnership set up by the FDA and Duke University to identify ways to improve the quality and efficiency of clinical trials. The researchers found the trials tended to be small, early-phase trials that were less robust than trials for therapies in other disease areas. Often, the oncology trials had no control/comparator and were non-randomized.

Tanning beds – FDA tightens oversight

The FDA proposed warning labels for tanning beds and sunlamps that advise (a) no one younger than 18 should use them, though they are not banned from using them, and (b) users are at risk of developing skin cancer. The FDA also proposed reclassifying the devices as moderate-risk products, which means that FDA 510(k) clearance would be needed before they are allowed on the market. The FDA will accept comments on the proposed order for 90 days.

REGULATORY NEWS

CMS opens the curtain on hospital charges

Health and Human Services (HHS) Secretary Kathleen Sebelius announced a three-part initiative that, for the first time, gives consumers information on what hospitals charge. The data showed significant variations across the country and within communities in what hospitals charge for common inpatient services. For example:

- Total joint replacement varies from $5,300 at a hospital in Ada OK to $223,000 at a hospital in Monterey Park CA.
- Heart failure charges range from $21,000 to $46,000 at different hospitals in Denver, and from $9,000 to $51,000 in Jackson MS.
- A pacemaker cost ~$26,000 at a Jackson MS hospital and more than $57,000 at the University of Mississippi Medical Center in the same city.
- The national average charge for COPD is $18,064, but the national average Medicare payment is $4,946.

FDA approvals/clearances

- **ARCOS' Burn Navigator** was cleared for use to guide the treatment of seriously burned patients during the fluid-intake phase.
- **BIOTRONIK's Ilesto 7**, the company's next-generation product in its line of implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy defibrillators (CRT-Ds), was cleared for use.
- **BRISTOL-MYERS SQUIBB's Sustiva (efavirenz)** was approved for use in HIV+ children as young as 3 months by opening the capsule and adding it to food/drink for patients who cannot swallow capsules or tablets.
- **COMBAT MEDICAL SYSTEMS' Combat Ready Clamp** was cleared for use in treating junctional hemorrhage on the battlefield or any other emergency situation.
- **EXACTECH's Gibralt Occipital Spine System** was cleared for use.
- **GLAXOSMITHKLINE and THERAVANCE's Breo Ellipta (fluticasone furoate + vilanterol inhalation powder)**, a combination of an inhaled corticosteroid (ICS) and a long-acting beta2-adrenergic agonist (LABA), was approved for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is also approved to reduce

exacerbations of COPD in patients with a history of exacerbations. Breo was given a boxed warning that LABAs increase the risk of asthma-related death. The FDA is requiring a patient medication guide with instructions for use and information about the drug's potential risks.

- **GLOOKO's diabetes management package** – The Glooko iPhone app was cleared for use to help patients keep track of food and drug intake, and the **MeterSync Cable** enables 19 different blood glucose meters to connect to an iPhone.
- **JOHNSON & JOHNSON's Sedasys**, a device used to allow patients undergoing a test such as a colonoscopy to be injected with the sedative propofol without the need for a doctor to monitor administration, was cleared for use. The company plans a limited release in 2014.
- **MASIMO's rainbow Acoustic Monitoring sensor**, the RAS-125c Acoustic Respiration Cloth Sensor, received 510(k) clearance for use to monitor respiration rate continuously and non-invasively in children.
- **MAUNA KEA TECHNOLOGIES' AQ-Flex 19 system**, an optical biopsy miniprobe for examining pancreatic cysts in patients undergoing endoscopic needle aspiration procedures in the digestive tract, received 510(k) clearance.
- **MEDTRONIC's Viva system**, an implantable cardiac resynchronization device, was cleared for use.
- **MERCK's Liptruzet (ezetimibe + generic atorvastatin)** was approved to lower high LDL and high triglycerides and to increase low HDL.
- **NOVARTIS' Ilaris (canakinumab)**, a monoclonal antibody targeting interleukin-1 beta, was granted expanded approval to treat systemic juvenile idiopathic arthritis (JIA).
- **WARNER CHILCOTT's norethindrone acetate + ethinyl estradiol chewable tablets and ferrous fumarate tablets** – This oral contraceptive was approved and is expected to be available in August 2013.
- **X-SPINE's Zygafix Facet Fusion System**, which is implanted using a minimally-invasive procedure to help stabilize a facet joint, was cleared for use.

FDA recalls/warnings

- **ABBOTT's Depakote (divalproex sodium) and related valproate products** – The FDA issued a warning that pregnant women should ***never*** use these agents to treat migraine headaches because they can decrease IQ scores in the baby. The drugs already carried a boxed warning for fetal risk, including birth defects, but now they are contraindicated for migraine treatment at any time during pregnancy. However, the drugs are also approved to treat epilepsy and manic episodes associated with bipolar disorder, and the FDA said they should only be used in those disorders if nothing else works.
- **BIOCOMPATIBLES' Patient-Specific Radioactive Brachytherapy Needle Sets** – The company received a warning letter that these devices do not conform to current good manufacturing practice (cGMP) requirements, including issues with validation, and the FDA rejected the company's plan to complete changes by September 30, 2013, saying that was too long since there have been "serious complaints."
- **CARDINAL HEALTH's Presource Kits** – The company initiated a Class I recall of these kits because the preassembled anesthesia circuit and filter may contain outer plastic packaging on one or more components. If the packaging is removed without disassembling the components, remnants of the plastic from the packaging material could become lodged in the filter, potentially causing an obstruction in airflow that could lead to hypoxia, suffocation, and death.
- **CARE DIAGNOSTICA's IVD Test Kits** – The company received a warning letter that the Austrian plant that makes these kits is not in conformity with cGMP requirements, including problems with quality, design, recordkeeping, and validation.
- **THE COMPOUNDING SHOP** – The FDA warned healthcare providers, hospitals, and pharmacies that it is concerned about sterility at this St. Petersburg FL compounding pharmacy and asked the company to remove all of its sterile products from the market, and the company is doing that.
- **COVIDIEN's Endo GIA Articulating 60-3.5 Surgical Stapler Reloads** – The FDA issued a warning that one lot of these devices was stolen from Covidien before being sterilized. Although the devices were packaged and labeled as sterile, they had not yet been sterilized, and some have apparently been offered for sale, so the FDA is urging healthcare providers to check the reference code and lot number on every box prior to use.
- **INTUITIVE SURGICAL's da Vinci** – The company issued an "urgent medical device notification" alerting hospitals that there is a "potential issue" with one of this surgical robot's instruments that can cause internal burns. Apparently, "micro-cracks" in some models of Intuitive's monopolar curved scissors can cause leaks that may "create a pathway for electrosurgical energy to leak to tissue" during use and potentially cause thermal injury. Making the situation more complicated, the micro-cracks may not be visible to the user.

- **MAQUET's SERVO-i Ventilator Battery Module** – The company initiated a Class I recall because the battery run time is shorter than expected, which could result in unexpected ventilator shutdowns, leading to serious adverse health consequences and even death.
- **ROCHE/GENENTECH's Kadcyla (ado-trastuzumab emtansine)** – The FDA issued a Drug Safety Communication warning of possible medication errors due to generic name confusion with Herceptin (trastuzumab). The FDA urged doctors to use both the brand and generic name on prescriptions to avoid confusion.
- **XYMOGEN's artriphen** – The company issued a recall of this nutraceutical used to aid in healthy joint function because it was found to contain traces of two undeclared allergens – soy and milk.

European regulatory news

- **Public access to clinical data.** The European Medicines Agency (EMA) announced a timetable for its policy on publicly releasing medical data from clinical trials. The EMA plans to release the draft policy in June 2013, receive public comments through September 2013, and publish its final policy at the end of November 2013, with implementation scheduled for January 2014. The final policy will take into account rulings on court cases challenging data transparency mandates, including a recent European Union interim court injunction in favor of pharmas **AbbVie** and **InterMune**. The EMA said its final policy will balance public health interests with the need for patient confidentiality and protection of intellectual property rights.
- **ARENA PHARMACEUTICALS' Belviq (lorcaserin)** – The company pulled its application with the European Medicines Agency's Committee for Medicinal Products for Human Use for this diet drug after regulators raised questions about tumors in rats, psychiatric events, and heart valve disorders.

U.K.'s National Institute for Health and Care Excellence (NICE) News

NICE is taking over healthcare IT. The National Health Service's Technology Adoption Centre will be administered by NICE and will be called the Health Technologies Adoption Programme. It will link the NHS in England with medical-device companies, encourage collaboration, and address obstacles to technology adoption.

Regulatory news from other countries

- ***Australia:*** The government is conducting a major review into the current funding scheme for chemotherapy drugs. While that is being done, Health Minister Tanya Plibersek said the government will provide A$29.7 million in order to pay doctors an additional A$60 per chemotherapy infusion for the next six months. The review was triggered because some oncologists said they could no longer afford to dispense a key chemotherapy drug because the entry of a generic had lowered the price so much.
- ***China:***
  - The National Health and Family Planning Commission announced new guidelines strengthening oversight of antibiotic use in hospitals and prescriptions in an effort to reduce drug-resistant disease. The new guidelines authorize the use of 50 types of antibiotics for top-level hospitals and 35 at second-level facilities. The commission estimated that the average amount of antibiotics used per person in China is ~10 times higher than in the U.S.
  - The China Food and Drug Administration set new licensing requirements for the manufacture of high-risk excipients, based on toxicity and dosage, as another step toward a drug master file system similar to the U.S. FDA's.
- ***India:***
  - The U.S. government put India on a trade blacklist over concerns about its lack of patent protection for pharmas.
  - The Drug Controller General's Office announced plans to inspect all of the country's clinical trial sites at least annually to verify regulatory compliance.
- ***Russia:*** Roszdravnadzor, the healthcare products regulator, is conducting a full review of its registration system after the arrest of one of its top officials on bribery charges. Previous product registrations are likely to remain valid. The review could result in a simpler, more transparent registration process.

2013 FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
May 22	Possible **reclassification of pedicle screws** used in spinal fusion surgeries	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
May 31	**Depomed's Sefelsa** (gabapentin extended-release), a hot-flash treatment (formerly known as Serada)	PDUFA date
June 5-6	**GlaxoSmithKline's Avandia** (rosiglitazone) – discussion of an independent readjudication by Duke University of the safety of this TZD in the RECORD trial	FDA's Endocrinologic and Metabolic Drugs Advisory Committee joint meeting with the Drug Safety and Risk Management Advisory Committee
June 13	Discussion of **when to submit a 510(k) for changes to existing devices**	FDA public meeting
June 13	**Possible reclassification of influenza detection devices** from Class I to Class II with special controls	FDA's Microbiology Devices Advisory Committee
June 20	**Dainippon Sumitomo Pharma/Sunovion Pharmaceuticals' Latuda** (lurasidone), a schizophrenia drug for use in treating bipolar disorder	PDUFA date
June 24-25	Discussion of the performance of **medical devices in women**	FDA public workshop
June 28	**Hisamitsu Pharmaceutical/Noven Pharmaceuticals' Pexeva** (paroxetine mesylate), a low-dose SSRI antidepressant to treat non-hormonal hot flashes in menopausal women	PDUFA date
July tba	**PET imaging** of brain beta-amyloid	CMS coverage decision expected
July 24	**SpinalMotion's Kineflex/C,** a metal-on-metal cervical artificial disc	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
July 25	**SpinalMotion's Kineflex Lumbar Artificial Disc,** a metal-on-metal lumbar artificial disc	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
July 28	**Aveo Pharmaceuticals** and **Astellas Pharma's Tivopath** (tivozanib) to treat advanced renal cell carcinoma	PDUFA date
August 17	**ViiV Healthcare's dolutegravir** for HIV	PDUFA date
September tba	**Sanofi/Genzyme's Lemtrada** (alemtuzumab) for multiple sclerosis	PDUFA date
October tba	**Gilead Sciences' sofosbuvir** + interferon and ribavirin to treat hepatitis C, genotypes 1-4-5-6, without interferon to treat genotype 2/3 ***and/or*** **Johnson & Johnson's simeprevir** + interferon and ribavirin to treat hepatitis C, genotype 1	FDA's Antiviral Drugs Advisory Committee
October 2	**Lundbeck** and **Takeda's Brintellix** (vortioxetine), an antidepressant for major depressive disorder	PDUFA date
October 3	**Pfizer** and **Ligand Pharmaceuticals' Aprela** (bazedoxifene/conjugated estrogens) to treat menopausal symptoms and osteoporosis prevention	PDUFA date
October 19	**Actelion's Opsumit** (macitentan), a dual endothelin receptor antagonist to treat pulmonary arterial hypertension	PDUFA date
October 21	**AMAG Pharmaceuticals' Feraheme** (ferumoxytol) expanded indication	PDUFA date
October 28	**Neos Therapeutics' NT-0202** (extended-release tablet formulation of amphetamine polistirex) to treat ADHD	PDUFA date
December 18	**GlaxoSmithKline** and **Theravance's Anoro** (umeclidinium bromide + vilanterol) for COPD	PDUFA date