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 **Centers for Medicare and Medicaid Services'** Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting to discuss Medicare's existing national coverage determination (NCD) for **ventricular assist devices (VADs)**.

SHORT TAKES

- **ALLERGAN** is buying a unit of **SkinMedica** that includes a prescription treatment for reducing female facial hair and wrinkle-reducing lotions.

- **AMARIN's Vascepa (icosapent ethyl, AMR-101) –** The FDA delayed its decision once again, this time for another month, on whether Vascepa is a new chemical entity (NCE), a designation that is important in determining how long, if at all, this omega-3 fatty acid will have exclusivity status.

- **AMGEN's Xgeva (denosumab) –** A study published in the ***Journal of Thoracic Oncology*** found that patients with advanced lung cancer had ***modest*** improvement in survival with Xgeva vs. **Novartis' Zometa** (zoledronic acid) – an improvement in median survival of 8.9 months vs. 7.7 months. A subgroup analysis found the benefit was driven by improved survival in patients with non-small cell lung cancer (NSCLC).

- **Glioblastoma –** A study by Ohio State University Comprehensive Cancer Center researchers – published in the journal ***Nature Medicine*** – found that the reason therapeutic (oncolytic) viruses have not been very effective in glioblastoma is because the patient's natural killer (NK) cells quickly blunt their effect. Their solution: block the immune response so the therapeutic virus can work. These were animal studies; the theory still has to be tested in humans.

- **PFIZER's Lyrica CR (pregabalin controlled-release) –** A long-acting formulation of Lyrica missed the primary endpoint in a Phase III trial, failing to decrease epilepsy seizure frequency. Pfizer said it will continue studies of Lyrica CR in fibromyalgia and post-herpetic neuralgia.

- **ROCHE/GENENTECH's Avastin (bevacizumab) –** The results of the AVANT trial, published in ***The Lancet Oncology***, do not support Avastin use in patients receiving oxaliplatin-based chemotherapy for resected Stage III or high-risk Stage II colorectal cancer, researchers concluded. Avastin failed to show an improvement in disease-free survival (DFS) vs. control, and Avastin patients had more relapses and deaths due to progression.

NEWS IN BRIEF

ACCUMETRICS' VerifyNow – possible new use?

If this platelet function test isn't useful for directing antiplatelet therapy in stent patients, maybe it will help in identifying stroke patients at greater risk. Australian researchers found that using this test to determine which patients are resistant to aspirin's antiplatelet effects may help identify patients at greater risk of a severe ischemic stroke.

The study, published in the ***Archives of Neurology***, found that patients admitted to the hospital who were identified by VerifyNow as aspirin-resistant were significantly more likely to have an NIH Stroke Scale (NIHSS) score of 16 or higher on admission (the definition of a severe stroke). In addition, resistant patients were more likely to have large infarctions.

Breast cancer – overdiagnosed?

A retrospective study of annual breast cancer data from the Surveillance, Epidemiology, and End Results database – published in the ***New England Journal of Medicine*** – found that mammography screening programs caused as many as 1.3 million women age >40 to be overdiagnosed with breast cancer over the past 30 years. The researchers concluded that overdiagnosis was involved in up to a third of all newly discovered tumors and that screening plays only a small role in reducing breast cancer mortality.

Screening programs, the researchers found, increased the detection of early-stage breast cancer but had little effect on the detection rate for late-stage disease. The implication: that many women underwent treatment for early breast cancer that might never have caused serious disease. Breast cancer mortality has been falling in the U.S., and the study implies that "treatment…is the main, if not the only, reason for the improvement."

The study has already become controversial. The American College of Radiology and the Society of Breast Imaging said: "The thesis…is simply wrong." Other experts noted that, even if there is a risk of overtreatment, it isn't clear yet which cancers need to be treated and which would be all right with watchful waiting.

Compounding pharmacies – pressure could lead to restrictions on other drugs

Public Citizen has called for an investigation by the Office of the Inspector General (OIG) of Medicare reimbursement policies that it claims "help fuel large-scale drug compounding." Public Citizen said, "CMS, through its inconsistent Medicare drug reimbursement policies concerning compounded drugs and decisions allowing routine coverage for such medication, appears to have created inadvertent financial incentives that helped large-scale production by compounding pharmacies to flourish."

Citing a 2007 decision by four regional Medicare Administrative Contractors, covering the entire country, to deny coverage for compounded inhalation drugs administered through a nebulizer, Public Citizen said CMS has the authority to prevent compounded drug coverage but has failed "to use this same authority to deny coverage for many other compounded drugs since then."

Will Avastin and other widely used compounded drugs now be in the crosshairs?

Primary hypersomnia – new cause, new cure

An Emory University School of Medicine study published in ***Science Translational Medicine*** found that an abnormal protein in cerebrospinal fluid appears to cause hypersomnia, a form of excessive daytime sleepiness, and that an already approved drug (flumazenil) can effectively treat it. Hypersomnia is different from narcolepsy in that patients do not necessarily fall totally asleep but remain in a sort of half-awake state.

Flumazenil, an intravenous GABA receptor signaling inhibitor, markedly reduced daytime sleepiness in seven patients tested. Since an IV drug with a short half-life is not very practical, the researchers developed sublingual and transdermal formulations that they gave to one patient over a 4-year period.

REGULATORY NEWS

FDA speeding up UDI requirement

The FDA is speeding up the requirements for unique device identifiers (UDIs) for implantable, life-supporting, or life-sustaining devices. All Class III devices and devices licensed under the Public Health Services Act still must have a UDI within ***one year*** of publication of the final rule. However, the FDA is now proposing to require all ***other*** implantable, life-supporting, and life-sustaining devices (i.e., those that are not already subject to the 1-year effective date) to have a UDI within ***two years*** of publication of the final rule instead of three years. That means that any Class II, Class I, or unclassified devices must comply sooner than originally expected (2 years instead of 3 years).

The new proposed rule also requires direct marking of the UDI on certain limited categories of devices, including implantable devices, within two years of finalizing the rule – instead of 3 years for Class III, 5 years for Class II, and 7 years for Class I. Public comments about the proposed rule closed on November 7, 2012. It is not clear when the FDA will issue the final rule.

FDA approvals/clearances

- **GLAXOSMITHKLINE and LIGAND PHARMACEUTICALS' Promacta (eltrombopag)** received expanded approval for use in hepatitis C patients with thrombocytopenia that makes them ineligible for interferon-based therapy.
- **HEARTWARE's HeartWare Ventricular Assist System (HVAD)**, a left ventricular assist device (LVAD), to support heart function and blood flow in patients with end-stage heart failure who are awaiting a heart transplant (bridge-to-transplant), was approved. This is the first time the FDA has approved an LVAD using registry data (in this case the INTERMACS registry) as the control.
- **NOVARTIS and DIAGNOSTICS GMBH's Flucelvax** was approved. It is the first seasonal flu vaccine manufactured using cell culture technology instead of the usual egg-based production method.
- **QUANTEL MEDICAL's SupraScan 577 laser system**, a solid-state yellow scanning laser to treat retinal conditions, was cleared for use.
- **RAIING's Wireless Thermometer**, a reusable thermometer sensor worn under the armpit, received 510(k) clearance. It sends real-time temperature data continuously via the Vitals Monitor iPhone app.
- **TOMTEC IMAGING SYSTEMS' Image-Com 5.0 software** received 510(k) clearance. The technology merges 3D and 2D images into a single viewer, offering interface with the company's radiology and cardiology applications for data analysis.

FDA recalls/warnings

- **HEARTSINE's Samaritan 300/300P** – A Class I recall of some (not all) of these public access defibrillators (PADs) was initiated because they were found to intermittently turn on and off, which could eventually deplete the battery.
- **INTEGRA NEUROSCIENCES' Intracranial Pressure Monitors and Ultrasonic Aspiration devices** – The FDA issued a warning letter that an inspection found these devices are not in conformity with current good manufacturing practice (cGMP) requirements.
- **ST. JUDE MEDICAL's Durata** – The FDA posted a 483 inspection letter (reported in October 2012) that gave more clarity about the design verification and validation flaws the Agency found in its inspection of the plant making the Riata/Durata ICD leads. The problem appears not to be isolated to Riata but also to include Durata. *Watch for a warning letter to be issued.*

European regulatory news

- **ACTELION's Opsumit (macitentan)** – The European Medicines Agency (EMA) accepted the company's submission for this oral dual endothelin receptor antagonist to treat pulmonary arterial hypertension.
- **BAYER and JOHNSON & JOHNSON's Xarelto (rivaroxaban)** – The European Commission approved an expanded use of this antiplatelet drug to treat pulmonary embolism (PE) and to prevent the recurrence of deep vein thrombosis and PE.
- **BRISTOL-MYERS SQUIBB and PFIZER's Eliquis (apixaban)**, a blood thinner, was approved by the European Commission for a second indication – prevention of strokes and systemic embolisms in atrial fibrillation patients. It was already approved for preventing venous thromboembolisms (VTEs) in patients undergoing hip- or knee-replacement surgery. The FDA PDUFA date was extended twice and is now March 17, 2013.
- **IMAGINE EYES' rtx1 retinal camera** received a CE Mark. It is the first adaptive optics platform technology cleared for clinical use in Europe.
- **JOHNSON & JOHNSON's Zytiga (abiraterone acetate)** – The EMA's Committee for Medicinal Products for Human Use (CHMP) recommended an expanded approval for this prostate cancer drug to include androgen-deprivation failures.
- **NOVARTIS:**
  - **Bexsero** – CHMP recommended approval of this meningitis B vaccine.
  - **Exjade (deferasirox)** – CHMP recommended approval to treat chronic iron overload requiring chelation in patients with non-transfusion-dependent thalassemia syndromes who do not respond to deferoxamine.
- **ST. JUDE MEDICAL's Portico**, a transcatheter aortic valve implant (TAVI), received a CE Mark. A European study of a larger (25 mm) Portico valve is scheduled to start by the end of 2012.

- **SANOFI and REGENERON PHARMACEUTICALS' Zaltrap (ziv-aflibercept)** – CHMP recommended approval of this VEGF inhibitor to treat metastatic colorectal cancer in combination with chemotherapy.
- **SANOFI and ZEALAND PHARMA's Lyxumia (lixisenatide)** – CHMP recommended approval of this GLP-1 agonist to treat Type 2 diabetes.
- **TERUMO/HARVEST TECHNOLOGIES' SmartPReP 2 Bone Marrow Aspiration Concentration System** received expanded CE Mark approval to process concentrated blood cells at the point of care to be used in patients with end-stage critical limb ischemia.

Regulatory news from other countries

Canada: **PURDUE PHARMA's OxyContin (oxycodone)** – The Canadian health minister is allowing the approval process for generic OxyContin to proceed despite a plea from the provincial governments, which unanimously requested a delay in the approval until regulators could examine the abuse of oxycodone. The minister said the federal government will tighten licensing rules so that oxycodone distributors have to keep better track of where the drug goes. Starting in 2013, they will need to report spikes in sales and changes in distribution patterns, and she said she is open to further restrictions on the drug if Canada's provinces cannot control the generic version.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
2012		
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	**Theravance's Vibativ** (telavancin hydrochloride), to treat hospital-acquired pneumonia caused by Gram-positive bacteria	FDA's Anti-Infective Drugs Advisory Committee
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 5	Consideration of whether **external counter-pulsating** (ECP) **devices** and **intra-aortic balloon pumps** (IABPs) should remain Class III devices	FDA's Circulatory System Devices Advisory Committee
December 6	Consideration of whether nonroller-type **cardiopulmonary bypass blood pumps** should remain Class III devices	FDA's Circulatory System Devices Advisory Committee
December 7	**Zogenix's Zohydro ER** (hydrocodone bitartrate extended-release) for moderate-to-severe chronic pain	FDA's Anesthetic and Analgesic Drug Products Advisory Committee
December 10	**CoAxia's NeuroFlo** catheter for treating cerebral ischemia	FDA's Neurological Devices Advisory Committee Rescheduled from November 1 due to weather
December 15	**Human Genome Sciences' raxibacumab** to treat inhalation anthrax	PDUFA date
December 17	**Amarin's Vascepa** (icosapent ethyl, AMR-101), an omega-3 fatty acid pill	FDA NCE decision expected ***(extended from November 16, 2012)***
December 20	**Hemispherx Biopharma's Ampligen** (rintatolimod injection, poly I: poly C12U) to treat chronic fatigue syndrome (CFS)	FDA's Arthritis Advisory Committee
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
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 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 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 27	**Ariad Pharmaceuticals' ponatinib** for treatment-resistant leukemia	PDUFA date
March 28	**Biogen Idec's BG-12** (dimethyl fumarate) for multiple sclerosis	PDUFA date (extended from December 28, 2012)

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	more 2013	
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
June 20	**Dainippon Sumitomo Pharma/Sunovion Pharmaceuticals' Latuda** (lurasidone), a schizophrenia drug for use in treating bipolar disorder	PDUFA date
July 28	**Aveo Oncology** and **Astellas Pharma's tivozanib** to treat advanced renal cell carcinoma	PDUFA date