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 **San Antonio Breast Cancer Symposium** in, yes, San Antonio, as well as the **American Society of Hematology** meeting in Atlanta.

SHORT TAKES

- **AMARIN's Vascepa (icosapent ethyl) –** The company apparently hasn't found a partner for this prescription omega-3 fish oil, is hiring a sales force, and will launch the drug itself in 1Q13.

- **AMGEN and PFIZER's Enbrel (etanercept) –** A study presented at the mid-year meeting of the American Society of Health-System Pharmacists (ASHP) found that Enbrel is more cost-effective in treating rheumatoid arthritis (RA) when screening, monitoring, and treating adverse events are included than either **Abbott's Humira** (adalimumab) or **Johnson & Johnson's Remicade** (infliximab) – $22,562/year vs. $43,948/year and $38,036/year, respectively.

- **BAXTER** is buying **Gambro**, which makes dialysis products for patients with acute or chronic kidney disease.

- **BAYER's Gadovist (gadobutrol) –** A >15,000-patient study presented at the Radiological Society of North America (RSNA) meeting found that this MRI contrast agent was safe and well tolerated, with only 0.53% of patients experiencing any drug-related adverse events (mostly nausea, dizziness, etc.).

- **BIODEL's glucagon** was granted orphan drug status by the FDA for the prevention of hypoglycemia in children with congenital hyperinsulinism.

- **CHELSEA THERAPEUTICS' Northera (droxidopa) –** The company said this investigational drug for hypotension met the primary endpoint in a 174-patient study, reducing dizziness and fainting during the first week. However, after that, the effect of the drug waned. The FDA in July 2012 requested another trial before approval. This study in neurogenic orthostatic hypotension showed efficacy and safety similar to an earlier study, but it is unlikely to be sufficient to meet the FDA's data demand.

- **COGNOPTIX's Sapphire II –** The company (formerly **Neuroptix**) exclusively licensed this eye-scanning test to detect and diagnose Alzheimer's disease – by measuring beta-amyloid in the supranuclear region of the lens of the eye – from the University of California, San Diego. The Sapphire II system consists of a laser-based reading device and consumable ophthalmic ointment. The eye exam can be given by a general practitioner in just a few minutes. It has not yet been cleared by the FDA.

- **DARA BIOSCIENCES' KRN-5500** – The company submitted an application to the FDA seeking orphan drug status for this investigational treatment for a painful form of chronic chemotherapy-induced peripheral neuropathy.

- **DENDREON's Provenge (sipuleucel-T)** – Georgia Health Sciences University is recruiting patients for a trial to test survival with this prostate cancer immunotherapy in combination with **CureTech's CT-011** and cyclophosphamide.

- **Diet drugs** – **GlaxoSmithKline**'s R&D chief predicted that GLP-1 agonists – e.g., **GSK's albiglutide** and **Novo Nordisk's Victoza** (liraglutide) – will ***not*** be approved by the FDA to treat obesity because of questions about efficacy.

- **Ear infections** – A mouse study published in the journal ***Laryngoscope*** found that systemic injections of an anti-granulocyte/macrophage colony-stimulating factor (GM-CSF) might be a novel way to treat intractable otitis media. The study found that inhibiting GM-CSF successfully reduced middle-ear inflammation induced by lipopolysaccharides – at least in mice.

- **ENDO HEALTH SOLUTIONS' Opana (oxymorphone)** – The company, seeking to have the original extended-release formulation declared "unsafe," sued the FDA. Endo replaced it with a more tamper-resistant formulation and is arguing that the FDA should not approve a generic of the original formulation.

- **Epilepsy drugs** – A study presented at the American Epilepsy Society's meeting found that generic extended-release epilepsy drugs are equivalent to branded versions, even if some generic immediate-release drugs are not. After reviewing data from 53 studies of 25 generic extended-release drugs – including phenytoin, carbamazepine, levetiracetam, and divalproex – the researchers concluded that there was considerable variability in the C_{max} and area under the curve, but "the products could be interchanged without danger to patients."

- **JOHNSON & JOHNSON's Xarelto (rivaroxaban)** – A study reported at the ASHP meeting found that this oral Factor Xa inhibitor is both effective and cost-effective in preventing deep venous thrombosis (DVT) after hip or knee replacement surgery vs. warfarin or **Sanofi's Lovenox** (enoxaparin). The researchers estimated that the cost savings with the use of Xarelto was $208.94 for a 35-day course of treatment in hip replacement surgery and $350.69 for a 14-day course post-knee arthroplasty.

- **LILLY** is collaborating with **Strides Arcolab** of India to manufacture generic cancer drugs. Strides' **Agila Specialties** will produce the drugs, and Lilly will market them.

- **LUNDBECK's AE-58054** – The company's CEO said Phase III trials will probably start in mid-2013 whether or not the company has found a partner for this Alzheimer's drug.

- **MEDTRONIC's DBS** – Five-year follow-up from the 102-patient SANTE study, presented at the American Epilepsy Society meeting, found that deep brain stimulation (DBS) was effective in patients with severely refractory partial-onset seizure epilepsy, with reductions of up to 69% in seizure frequency. The device is approved for this indication in Canada and Europe, but the FDA rejected this indication in 2010.

- **MERCK KGAA/MERCK SERONO** is partnering with Abu Dhabi-based **Neopharma**, which will produce two of Serono's brand-name medications in the United Arab Emirates – Euthyrox (levothyroxine), a synthetic hormone therapy for hypothyroidism, and Glucophage (metformin) for Type 2 diabetes. Production is expected to begin in 2013.

- **MERCK's MK-8931** – The company said it started a 1,700-patient, two-phase Phase II/III trial of this oral BACE inhibitor that targets beta-amyloid in Alzheimer's disease. The first phase will enroll 200 patients with early Alzheimer's.

- **Metformin** – A 239-patient study published in the journal ***Cancer*** found that metformin, a diabetes drug, may prevent or treat ovarian cancer. The study found that women with ovarian cancer who took metformin for diabetes actually had 20% better survival vs. women who did not take metformin (67% alive at 5 years vs. 47% with control). The mechanism of action is not known. The researchers said the findings support going forward with a larger trial.

- **MIRACOR MEDICAL SYSTEMS' PICSO** – The 10-patient, non-randomized study published in the ***Journal of Interventional Cardiology*** found this system improved myocardial perfusion following percutaneous coronary intervention (PCI) in STEMI patients, and the improvements were sustained for 90 minutes, which was the goal. A new 40-patient study, Prepare RAMSES, is already under way.

- **RECKITT BENCKISER's Suboxone (buprenorphine + naloxone)** – The requirement that patients in treatment programs have to wait a year to be eligible to receive a two-week supply of this anti-addiction drug has been lifted. The waiting period still applies to methadone.

- **Steroid injections for back pain** – A small study published in the journal ***Spine*** found that postmenopausal women who get injections of triamcinolone acetonide in the

spine for lower back pain had an increased risk of bone loss in their hips. Women who got the injections lost six times as much bone mineral density (BMD) at the hip as women who didn't, although the absolute difference was small (0.018 g/cm^2 vs. 0.003 g/cm^2, p=0.007). The researchers recommended that doctors be cautious about giving the injections to older women at higher risk of osteoporosis.

- **ZOGENIX's Zohydro (hydrocodone)** – The FDA's Anesthetic and Analgesic Drugs Advisory Committee voted 11-2 against recommending approval of this pure hydrocodone product, citing concens about its abuse potential.

NEWS IN BRIEF

ACCUMETRICS' VerifyNow – study suggests no value to aspirin-resistance testing

A 400-patient study published in ***Circulation: Journal of the American Heart Association*** found that aspirin resistance is so rare that the University of Pennsylvania researchers were unable to identify even one case of true aspirin resistance, raising questions about the value of point-of-care diagnostic testing for aspirin resistance. The researchers said the lack of a mechanism of action to explain aspirin resistance suggests there is no genetic basis for it, just a pharmacokinetic explanation. They postulated that "pseudoresistance" actually delayed/reduced absorption due to coatings on some aspirins.

In one part of the study – which was supported by the National Heart, Lung, and Blood Institute, the American Heart Association, and Bayer – responders and initial non-responders were re-tested, and the non-responders did not necessarily remain non-responders, with half the non-responders becoming responders four hours later and even more becoming responders eight hours later. And none of the patients who received uncoated aspirin were non-responders.

AMGEN's Aranesp (darbepoetin) – one way to cut use and improve outcomes

A pharmacist from an Illinois hospital reported – in a poster presented at the ASHP meeting – how her hospital dramatically cut the over-use (and expense) of this erythropoietin-stimulating agent (ESA) by giving pharmacists control of use in hospitalized patients with anemia associated with chronic kidney disease.

The savings were achieved by decreasing the average Aranesp dose (from 160-200 µg to 60 µg) and eliminating the inappropriate use (e.g., postoperative anemia) while nearly doubling IV iron use. And the savings did not come at the expense of patient care; the new protocol actually improved average hemoglobin levels in patients.

Benzodiazepines – increase the risk of pneumonia and death

A study of 4,964 cases of community-acquired pneumonia in the U.K. Health Improvement Network database – and published in the journal ***Thorax*** – found that these anti-anxiety drugs may increase the risk of contracting and dying from pneumonia. In particular, **Valium**, **Ativan**, and **Restoril** – but not librium – were associated with an increased incidence of pneumonia. All four drugs were associated with an increased long-term risk of death. However, the researchers said their findings do not definitively prove that benzodiazepines cause pneumonia and recommended additional studies.

QUESTCOR PHARMACEUTICALS' Acthar (adrenocorticotropin hormone, ACTH) – prednisolone a better alternative for infantile spams

A 30-infant pilot study presented at the American Epilepsy Society meeting found that high-dose (8 mg/kg/day) prednisolone is effective in clearing most infantile spams within two weeks, avoiding the need for the much more expensive Acthar. In the study, 60% of the babies had a complete response, with slightly less than half responding to Acthar when switched to that. However, this was not a head-to-head trial of prednisolone vs. Acthar.

ROCHE's Zelboraf (vemurafenib) – is the survival improvement worth the cost?

A study presented at the ASHP meeting found that the cost of treating a metastatic melanoma patient with this BRAF inhibitor improved 6-month survival (from 64% to 84%) but at a cost of ~$10,000/month vs. dacarbazine. The study questioned whether the cost can be justified in a state Medicaid program. The researcher estimated that treating 11 cases/year of metastatic melanoma with dacarbazine would cost $31,873/year vs. adding Zelboraf, which would increase the cost to $314,347/year.

Smartphones – nurses use them on the job at most hospitals

A study by Spyglass Consulting Group, a market intelligence and consulting firm, found that nurses at 69% of hospitals surveyed (by telephone) are using smartphones on the job for both personal and clinical communications, but the hospital information technology (IT) departments are not willing to

support the devices on the hospital's network because of concerns about the security of patient health information.

Other findings in the survey included:

- Nurses at 96% of hospitals believe that first-generation tablet PCs are not the right device for bedside nursing.
- Nurses predicted the iPad will not be successful for bedside nursing because of concerns about durability, infection control, limited data entry, and lack of appropriate applications.
- Nurses at 25% of hospitals were dissatisfied with the quality and reliability of the wireless network within their hospitals.

TEVA PHARMACEUTICAL – reorganizing

Looming competition for several key products has prompted Teva to reorganize. Among the planned changes are:

- Streamlining operations.
- Cutting $1.5 billion to $2 billion in costs.
- Making targeted acquisitions in core areas of expertise, such as central nervous system disorders.
- Discontinuing some research programs – though Teva didn't say which programs.
- Continuing to invest in treatments for multiple sclerosis and other central nervous system disorders.

REGULATORY NEWS

Court: off-label drug marketing a free-speech right

The 2nd Circuit U.S. Court of Appeals in New York overturned the conviction of a former sales rep for Orphan Medical (now part of **Jazz Pharmaceuticals**) for off-label drug marketing of Xyrem (sodium oxybate), saying the conviction violated his First Amendment free-speech rights. The court cited a 2011 Supreme Court ruling in Sorrell v. IMS Health that cited free-speech rights in overturning a Vermont law restricting pharmaceutical companies from using prescription data for marketing purposes. The ruling could threaten FDA rules that prevent off-label marketing.

FDA collaborates with medical device companies

The FDA and device manufacturers collaborated to form the Medical Device Innovation Consortium (MDIC), a non-profit, public/private partnership designed to work together and with patient advocacy groups, the Centers for Medicare & Medicaid Services (CMS), foundations, and academia to speed device approvals safely. The organization was first started by LifeScience Alley, a Minnesota-based industry group, but the FDA decided to participate.

Among the companies participating are **Abiomed**, **Becton Dickinson**, **Boston Scientific**, **Cyberonics**, and **Medtronic**. The consortium will be governed by a national board of directors, including industry executives and government leaders. The initial head will be Maura Donovan, PhD, former vice president of therapy research and development at Medtronic. MDIC will be funded largely by device companies, but the FDA and CMS may contribute funding later.

MDIC will invest in projects that could reduce the time and costs involved in medical device development. No specific projects have been announced yet. MDIC's first meeting is expected in 1Q13.

FDA gives PET drugs three years to get approved

The FDA issued guidelines on the steps that must be taken by manufacturers of positron emission tomography (PET) drugs that are used in a clinical environment to get their drugs approved. The Agency set a December 12, 2015, deadline for the companies to submit a new drug application (NDA), abbreviated new drug application (ANDA), or investigational new drug (IND) application, and get their products approved.

PhRMA challenging local drug take-back ordinance

The Pharmaceutical Research and Manufacturers of America (PhRMA), the Biotechnology Industry Organization (BIO), and the Generic Pharmaceutical Association filed a lawsuit in the U.S. District Court for the Northern District of California to try to block a local law that requires drug companies to submit plans for take-back programs by July 1, 2013. PhRMA claims the ordinance violates the Constitution because it interferes with interstate commerce, will not help much with fighting drug abuse, and may make collection points targets for thieves and drug abusers.

FDA approvals/clearances

- **ALIVECOR's iPhone electrocardiogram app** was approved. The $199 mobile ECG heart monitor uses electrodes that snap onto the back of an iPhone 4 or 4S, taking readings from a person's fingers or chest.
- **CYNOSURE's PicoSure**, a tattoo-removal laser, was cleared for use. The company said that, starting early next year, it

plans to sell the laser through its direct sales force to aesthetic dermatologists and plastic surgeons in the U.S.

- **DEVICOR MEDICAL PRODUCTS' Mammotome revolve** – The FDA cleared this updated biopsy system.
- **IRIDEX's TxCell system**, which allows the company's photocoagulation laser to be administered in a multi-spot scanning fashion, received 510(k) clearance.
- **IVERA MEDICAL's Curos Tips**, disinfection tools for male luer connectors used to deliver IV drugs, received 510(k) clearance.
- **NEUROMETRIX's disposable electrode** for its **Sensus** pain management device (which treats painful diabetic peripheral neuropathy with electromagnetic nerve stimulation) was cleared.

FDA recalls/warnings

- **BUNNELL's Life Pulse High-Frequency Ventilator Patient Circuits** – The company instituted a nationwide recall due to a potential failure risk.
- **ENDO HEALTH SOLUTIONS/QUALITEST's hydrocodone bitartrate and acetaminophen tablets (USP 10 mg/500 mg)** – A voluntary nationwide recall of 101 lots was initiated due to the potential for tablets with a too-high dose.
- **GLAXOSMITHKLINE's Zofran (ondansetron hydrochloride)** – The 32 mg single IV dose of this drug to prevent chemotherapy-induced nausea and vomiting was pulled from the market due to the potential for QT prolongation and torsades de pointes. The FDA does not expect this withdrawal to create a shortage of IV ondansetron because the Agency said the 32 mg dose accounts for a very small percentage of the current market. The FDA continues to recommend use of the 0.15 mg/kg dose, administered every four hours for three times.
- **Heparin** – The FDA issued a Drug Safety Communication, warning healthcare professionals and patients that heparin container labels are being changed to state more clearly the total drug strength. The new labels, aimed at reducing medication errors, will say how much Heparin is in 1 mL.
- **SHANGHAI HUHUI DAILY USE CHEMICAL PRODUCTS** received a warning letter for several violations, including redacting production records. The FDA said the company's actions "raise serious concerns regarding the integrity, reliability, and traceability of the data generated and documented" in the company's records.

European regulatory news

- **BIOVENTRIX's Revivent Myocardial Anchoring System**, which is used to improve ventricular action in congestive heart failure patients, received a CE Mark.
- **MEDTRONIC's Sentrino** continuous glucose monitoring system received a CE Mark.
- **ZHENGZHOU TIANJIE ELECTRONIC EQUIPMENT's Tianjie Dental Falcon** – The U.K.'s Medicines and Healthcare products Regulatory Agency is asking the National Health Service and private dentists not to use this hand-held x-ray machine on patients, saying it is unsafe and poses a significant health risk by exposing users and patients to 10 times the normal level of radiation because the lead shielding inside is insufficient.

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

- **NICE** said that pharmas have been giving the U.K. steep discounts (up to 50%) to get NICE approval of their drugs.
- **ALIMERA SCIENCES' Iluvien (fluocinolone acetonide intravitreal implant)** – NICE recommended against the National Health Service's use of this intravitreal implant for diabetic macular edema (DME), citing cost. NICE's independent Appraisal Committee found that the cost per quality-adjusted life year (QALY) gained was at least £47,600 (US$76,350).
- **PFIZER's Inlyta (axitinib)** – NICE rejected this renal cell carcinoma drug for use in patients who failed Pfizer's **Sutent** (sunitinib), saying (a) Pfizer's comparator wasn't approved by NICE and (b) the trial didn't compare Inlyta to best supportive care. So, NICE wants to see more data showing that Inlyta has a robust effect and is cost-effective.

Regulatory news from other countries

- ***Canada:***
  - **ASTRAZENECA** and **PFIZER** are partnering with the Quebec provincial government on "a new approach to drug development as a public-private partnership," creating the Neomed Institute, a new life-sciences research facility in Montreal. The goal is to bridge the gap between early-stage research and later-stage drug development.
  - **CHEMI PHARMACEUTICAL**, a Canada-based contract laboratory, had its license suspended by Health Canada for falsifying test results. Companies that were customers of Chemi were asked to suspend all sales of products tested by Chemi until their safety can be confirmed.

- **SANOFI PASTEUR's Menactra meningococcal vaccine** received expanded approval to include people age 9 months to 55 years.
- **VERTEX PHARMACEUTICALS' Kalydeco (ivacaftor)** was approved to treat cystic fibrosis patients with the G551D mutation.

■ ***China:*** **EDWARDS LIFESCIENCES' Carpentier-Edwards Perimount device**, a mitral valve made of bovine pericardial tissue, was approved by the State Food and Drug Administration.

■ ***Japan:***

- **NOVO NORDISK's Ryzodeg (insulin degludec/ insulin aspart)** received initial approval of an advisory committee to the health ministry.
- **SORIN GROUP's Mitroflow aortic heart valve** was approved.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
2012		
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 Sirturo** (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	**Boehringer Ingelheim's Striverdi Respimat** (olodaterol) for chronic obstructive pulmonary disease (COPD)	FDA's Pulmonary-Allergy Drugs Advisory Committee
January 29	**Sanofi/Genzyme** and **Isis Pharmaceuticals' Kynamro** (mipomersen) for homozygous familial hypercholesterolemia	PDUFA date
January 30	**Pharmaxis' Bronchitol** (mannitol inhalation powder) for the management of cystic fibrosis	FDA's Pulmonary-Allergy Drugs Advisory Committee
January 30	**Raptor Pharmaceutical's cysteamine bitartrate** delayed-release (RP-103) to treat nephropathic cystinosis	PDUFA date
February 2	**Hemispherx Biopharma's Ampligen** (rintatolimod injection, 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)
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 Tivopath** (tivozanib) to treat advanced renal cell carcinoma	PDUFA date