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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SHORT TAKES

- **ALLERGAN's Lap-Band –** The marketing firm 1-800-GET-THIN and several healthcare providers were sued by a woman who suffered complications from a Lap-Band procedure in 2011 that required removal of her stomach. The suit is aimed at the doctors, the hospital, and the advertiser – not the device.

- **ATOX BIO's AB-103**, an investigational treatment for necrotizing soft-tissue infections, was granted fast track status by the FDA.

- **BIODELIVERY SCIENCES INTERNATIONAL's BEMA buprenorphine/naloxone (BNX) –** The company said this opioid-dependence treatment met the primary endpoint in a pharmacokinetic (PK) study performed at the FDA's request, with absorption levels similar to that achieved with **Reckitt Benckiser's Suboxone** (buprenorphine and naloxone), which is already approved to treat opiate addiction.

- **CLEVELAND BIOLABS' Entolimod (CBLB-502) –** The company said the FDA sent a letter "indicating agreement" with the company's preclinical animal studies of this investigational drug designed to reduce the risk of death after total body irradiation (e.g., a nuclear attack or accident).

- **CORNERSTONE THERAPEUTICS/CARDIOKINE BIOPHARMA's Lixar (lixivaptan, CRTX-080) –** The FDA's Cardiovascular and Renal Drugs Advisory Committee voted 8-0 against using Lixar to treat symptomatic hypervolemic and euvolemic hyponatremia related to congestive heart failure and 5-3 against using it to treat the syndrome of inappropriate antidiuretic hormone (SIADH). Of particular concern to the panel was the potential use of the drug outside a hospital and the need for close monitoring of patients getting the drug. The PDUFA date is October 29, 2012.

- **Drug-eluting stents (DES) –** In a ***CRTonline.org*** survey, 74% of respondents said a DES with a biodegradable polymer and 6 months of dual antiplatelet therapy is more appealing than a DES with a durable polymer and 3 months of dual antiplatelet therapy (26%).

- **DUNE MEDICAL DEVICES' MarginProbe –** Researchers reported at the Multidisciplinary Breast Cancer Symposium that this device can reduce re-excision after breast-conserving breast cancer surgery. The operating-room device – which emits a biomagnetic signal and assesses tissue response to the signal, helping doctors to determine whether the surgical margins are clear – was associated with a >50% reduction in re-excisions for ductal carcinoma *in situ* (DCIS) – a re-excision rate of 13% vs. 37% without it. The FDA's General and Plastic Surgery Devices Advisory Committee

recommended approval of the device in June 2012, and an FDA decision is expected soon.

- **GERON's imetelstat** – The company said it is discontinuing a Phase II trial of this investigational breast cancer drug because an interim analysis indicated there was no benefit vs. control (standard chemotherapy), with median survival of 6.2 months vs. 8 months in control. In addition, there was an excess of deaths in the imetelstat arm (16 vs. 10). A Phase II trial is continuing in non-small cell lung cancer (NSCLC), though the company is not optimistic about the outcome in that cancer either.

- **JOHNSON & JOHNSON's Xarelto (rivaroxaban)** – The company said it gave the FDA "additional data" from the ATLAS trial relating to its application for a supplemental indication to prevent a second heart attack or stroke in patients at high risk because of coronary artery stenosis and to prevent in-stent restenosis. In June 2012, the FDA rejected this indication after the Cardiovascular and Renal Drugs Advisory Committee expressed concern about bleeding side effects, but J&J is trying again.

- **LIFEIMAGE** – The company, which is an electronic imaging sharing business, said the FDA finished its initial inspection.

- **LIGOCYTE PHARMACEUTICALS' Norovirus VLP vaccine** – A Phase I/II proof-of-principle study in 75 healthy adults found that this investigational injectable vaccine against norovirus was safe and that it stimulated an immune response.

- **LUNDBECK and OTSUKA's aripiprazole depot** – The company resubmitted this investigational schizophrenia drug to the FDA, and the PDUFA date is February 28, 2013. The FDA rejected the drug in July 2012, issuing a complete response letter that cited deficiencies at the contract manufacturer.

- **MERCK's Proscar (finasteride)** – An NCI-funded study, published in the ***Journal of the National Cancer Institute***, found that this synthetic type-2 5α-reductase inhibitor, which is used to treat benign prostatic hyperplasia (BPH), does not reduce quality of life – physical functioning, mental health, or vitality – when used long term.

- **NAVIDEA BIOPHARMACEUTICALS' Lymphoseek (99m-Tc-tilmanocept)** – The FDA rejected this radioactive agent used to trace lymph nodes in cancer patients, issuing a complete response letter that the company said raised cGMP issues relating to the third-party contract manufacturing, not efficacy or safety. Navidea plans to fix the problems and resubmit the drug.

- **NEURALSTEM's NSI-566 (a stem cell gel)** – A study by University of California, San Diego, researchers, published in the journal ***Cell***, reported that this stem cell treatment restored paralyzed rats' ability to move. In the study, researchers severed the spinal vertebrae of 12 rats and then gave half of them Neuralstem's stem cells. Reportedly, the rats that received the stem cells gained significant locomotor recovery. The company hopes that, given these findings, the FDA will lift the clinical hold it placed on the treatment in October 2010.

- **ONCOLYTICS BIOTECH's Reolysin (wild-type reovirus)** – The company said that IV Reolysin, in combination with carboplatin + paclitaxel, met the primary endpoint, showing a positive patient-response rate in the first half of a Phase II trial in squamous cell carcinoma of the lungs. Oncolytics now plans to go ahead with the second half of the trial. In addition, the company is increasing the size of its Phase III trial in head and neck cancers by ~50%.

- **ONYX PHARMACEUTICALS' Kyprolis (carfilzomib)** – A study published in ***Leukemia Research*** suggested that this drug, which is approved to treat patients with refractory multiple myeloma, may also have direct beneficial effects on bone. Researchers from Washington University found in a mouse study that both Kyprolis and Onyx's oprozomib (ONX-0912), an investigational oral drug, inhibited bone resorption and increased bone formation, independent of their effects on myeloma, blocking bone loss as well as decreasing tumor burden.

- **PALATIN TECHNOLOGIES and ASTRAZENECA's AZD-2820** – The companies are discontinuing development of this investigational obesity drug after a serious adverse event occurred, reportedly an allergic reaction.

- **PFIZER's dacomitinib (PF-00299804)** – **SFJ Pharmaceuticals** is going to conduct a Phase III trial for Pfizer of this oral, once-daily pan-HER inhibitor for lung cancer. SFJ is funding and supervising the trial, which will be conducted in Asia and Europe in patients with locally advanced or metastatic NSCLC and EGFR mutations.

- **PULMATRIX's PUR-118** – The company received a $1.4 million grant from the Cystic Fibrosis Foundation to help support studies of this BID, inhaled, anti-inflammatory drug for cystic fibrosis.

- **ROCHE/GENENTECH's Tarceva (erlotinib)** – A small multicenter study presented at the Chicago Multidisciplinary Symposium in Thoracic Oncology meeting found that Tarceva may slow recurrence in NSCLC patients with early-stage disease, with two-year disease-free survival >90% post-surgery.

- **SHIRE's Vyvanse (lisdexamfetamine dimesylate) –** The company submitted a supplemental new drug application (sNDA) to the FDA for use of Vyvanse as maintenance therapy in attention-deficit/hyperactivity disorder (ADHD) in children age 6-17. It already is approved for adults. The PDUFA date is April 29, 2013.

- **SUNOVION PHARMACEUTICALS' Latuda (lurasidone hydrochloride) –** The company submitted two sNDAs to the FDA for this drug – as adjunctive therapy and as monotherapy in adults with depressive episodes tied to bipolar I disorder.

- **Vaccines –** A study published in the ***New England Journal of Medicine*** found that the pertussis (whooping cough) vaccine loses efficacy over time. By the fifth yearly dose, children had a 42% increased risk of acquiring whooping cough, suggesting that this may explain recent outbreaks in the U.S., including 10,000 cases this year in children age 7-10. Health officials are considering recommending children get another booster shot.

- **ZALICUS' Synavive (CRx-102) –** The company is discontinuing trials of this investigational drug for rheumatoid arthritis after a Phase IIb trial found no significant benefit over prednisolone.

NEWS IN BRIEF

AMARIN's Vascepa (icosapent ethyl, AMR-101) – will negative news affect launch?

This omega-3 fatty acid supplement got FDA approval in July 2012 to lower high triglycerides and now competes with **GlaxoSmithKline's Lovaza** (omega-3 ethyl esters), but whether Vascepa ever gains broad use probably will depend on whether or not it reduces major cardiovascular events, and an outcomes study is under way. However, a Greek meta-analysis of 20 omega-3 studies covering 68,680 patients, published in the ***Journal of the American Medical Association***, found that omega-3 fatty acid supplements (not Vascepa specifically) did not reduce the risk of major cardiovascular events (all-cause mortality, cardiac death, sudden death, heart attack, or stroke). The researchers concluded: "Our findings do not justify the use of omega-3 as a structured intervention in everyday clinical practice or guidelines supporting dietary omega-3."

Heart rhythm devices – new guidelines

The American College of Cardiology Foundation, the American Heart Association, and the Heart Rhythm Society issued joint updated guidelines for the use of device-based therapies in treating heart rhythm disorders, with:

- Expanded indications for cardiac resynchronization therapy (CRT) to include patients with NYHA Class II heart failure, based on ECG results.
- Recommendations on which patients are most likely to benefit from CRT (e.g., wide LBBB).
- Guidance on which atrial fibrillation patients are likely to benefit from CRT.
- Minimum frequency of in-person and remote monitoring of patients with implantable devices.

Imaging

- French researchers have developed a computer program that turns images from CT scans into 3D pictures. A case report in the ***New England Journal of Medicine*** suggests the program could make surgery safer by helping doctors see things not apparent with normal CT images.
- British engineers have developed an ultrasound scanner that costs less than $64 to make. They are looking for a partner to commercialize it.
- A study presented at the American Society of Nuclear Cardiology meeting found that an advanced SPECT scanner had adequate image quality in the super-obese. However, a small study found that PET/CT imaging was better than SPECT in morbidly obese patients for determining myocardial perfusion and better correlated with angiographic findings.
  - Image quality was excellent 60% of the time with PET and 14% with SPECT.
  - The positive predictive value was 72.7% for PET and 26.2% for SPECT.
  - >70% of PET images had no attenuation artifacts vs. 19% of SPECT images.

Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

- **ABBOTT's Norvir (ritonavir).** The randomized, 296-patient ASSURE trial found that patients whose HIV was under control (HIV RNA <75 copies/mL) on **Gilead Sciences' Truvada** (tenofovir + emtricitabine) + **Bristol-Myers Squibb's Reyataz** (atazanavir) boosted with ritonavir could safely drop the ritonavir.

- **BIOGEN IDEC's Tysabri (natalizumab).** Researchers reported that ≥17 patients taking Tysabri have developed serious herpes simplex or varicella zoster infections since November 2004. Most of these patients required long hospitalizations and systemic antiviral therapy, and two died. CNS infections are a labeled risk for Tysabri, but the study highlights how serious these infections can be.
- **GILEAD SCIENCES**
  - **GS-7340 (tenofovir alafenamide, TAF).** Early data on this analog of **Viread** (tenofovir disoproxil fumarate), which is currently in Phase II development, suggested that it may be more potent at a lower dose and *perhaps* less toxic.
  - **Truvada (tenofovir + emtricitabine).** A study, not presented at ICAAC but published in the journal ***Science Translational Medicine***, found that missing a dose or two of this drug when used for HIV ***prevention*** does not appear to reduce the efficacy.
- **MERCK's MK-1439.** Preclinical data on this investigational non-nucleoside reverse transcriptase inhibitor (NNRTI), which is in Phase II development, indicated it is potent and active against many drug-resistant HIV strains that often cause other NNRTIs to fail. The issue with this drug may be resistance to the Y188L mutation.
- **VIIV HEALTHCARE and SHIONOGI's S/GSK-1265744.** Preliminary data suggested that this back-up compound to daltegravir may be able to be dosed monthly. And the data suggested it may have utility in prevention as well as treatment.

SANOFI PASTEUR's dengue fever vaccine – failed

The results – published in ***The Lancet*** – of a >3,600-child study conducted in Thailand showed that this vaccine missed the primary endpoint, showing only 30% efficacy. The vaccine, which is made of live, attenuated viruses, failed to protect against one (serotype 2) of the four strains of dengue virus. Over two years, 3% of vaccinated children got dengue fever vs. 4% of control. However, the vaccine was 60% effective against serotype 1 and ~80%-90% effective against serotypes 3 and 4 – with one innoculation. Sanofi said it is not giving up on the vaccine.

REGULATORY NEWS

Device helps FDA detect counterfeits

FDA Commissioner Margaret Hamburg, MD, said the Agency is using its Counterfeit Detection Device No. 3 (CD3) – a portable, hand-held, battery-operated device that sprays 10 different wavelengths of visible and invisible light over tablets, boxes, and documents – to help detect counterfeit products and documents because they appear a different color or shade. CD3 doesn't identify the problem, but it alerts the user that there is a discrepancy/difference. Currently, the FDA has ~50 CD3 devices in use in the field.

FDA proposes changes to postmarket device surveillance program

The FDA announced proposed changes to its postmarket surveillance system for medical devices that includes establishing a unique device identification system. The FDA's Center for Devices and Radiological Health (CDRH) proposed four initiatives to improve surveillance:

1. Implementing a unique device identifier (UDI) system that can integrate with electronic medical records.
2. Promoting the development of national and international registries for certain devices.
3. Modernizing adverse-event reporting and analysis.
4. Developing new methods for evidence generation, synthesis, and appraisal.

The FDA plans to hold four public meetings on the proposed initiatives and is also accepting public comments online.

HHS will not regulate Nationwide Health Information Network

The Office of the National Coordinator for Health Information Technology announced that it is backing off of an earlier decision to regulate the proposed nationwide health information network after experiencing major pushback from multiple organizations. ONC chief Farzad Mostashari, MD, said, "Our goal is to increase information exchange, not to hobble it or hinder it in any way, and it was something that we have to listen to carefully…We've decided that now is not the time, probably, to pursue a regulatory approach that follows what we laid out."

FDA approvals/clearances

- **ABIOMED's Impella Cardiac Power** (Impella cVAD outside the U.S.), the newest version of this catheter-based cardiac assist device, was granted 510(k) clearance.
- **ACCESS SCIENTIFIC's 4 Fr Nanopuncture Powerwand**, a peripheral IV catheter, received 510(k) clearance.
- **COVIDIEN's LigaSure** – which seals vessel walls without subjecting surrounding tissue to heat damage – was granted expanded 510(k) clearance for use during ear, nose, and throat procedures. It already had clearance for use in general surgery.
- **GENMARK DIAGNOSTICS' eSensor Respiratory Virus Panel**, which can identify and distinguish 14 viruses in patients with flu-like symptoms, received 510(k) clearance.
- **ICONACY ORTHOPEDIC IMPLANTS' I-Hip**, a total hip replacement system, was cleared for use.
- **MAYO CLINIC's Choline C 11 Injection**, a PET imaging agent designed to help detect recurrent prostate cancer, was approved by the FDA. The Mayo Clinic is the first facility approved to manufacture this IV agent.
- **PREVENTICE's BodyGuardian Remote Monitoring System** – The FDA approved this remote heart monitoring system that transmits a patient's ECG, heart rate, and respiration rate over a cellphone and allows doctors to review the data on their iPads. The system was developed in collaboration with the Mayo Clinic. The company plans to make the system available over-the-counter by the end of the year but will begin selling it to hospitals and clinics immediately.
- **SANOFI/GENZYME's Aubagio (teriflunomide)**, a once-daily oral drug, was approved to treat relapsing-remitting multiple sclerosis (MS). The label includes a boxed warning about possible liver problems and a risk of birth defects. Doctors are advised to do a liver function test before starting a patient on Aubagio and periodically thereafter. Aubagio is Pregnancy Category X, which means women of childbearing age must have a negative pregnancy test before starting the drug and must use effective birth control while taking it. The European Medicines Agency (EMA) is expected to make a decision on Aubagio in 1Q13.
- **TANGENT MEDICAL TECHNOLOGIES' NovaCath Secure IV Catheter System** for intravenous drug delivery received 510(k) clearance.

FDA recalls/warnings

- **APIA ENTERPRISE's contact lenses** – The company received a warning letter about improper medical device reporting procedures.
- **BIOMERIEUX** received a warning letter about manufacturing issues at the plant that makes its *in vitro* diagnostic devices.
- **ENDO HEALTH SOLUTIONS/QUALITEST's hydrocodone bitartrate + acetaminophen tablets** – One lot was recalled because it may have tablets with too high a dose of acetaminophen.

European regulatory news

- **ENDOLOGIX's Nellix EndoVascular Aneurysm Sealing System** for abdominal aortic aneurysms received a CE Mark.
- **NEUROSIGMA's Monarch** external Trigeminal Nerve Stimulation device, which is used to aid in treating major depression and epilepsy, was approved. The patient wears a disposable patch on the forehead that is linked to an external pulse generator that stimulates the trigeminal nerve.
- **RENEURON's ReN-001 and ReN-009** – The company asked the U.K. regulatory authority for permission to test both of these stem cell treatments in clinical trials – ReN-001 in a Phase II trial in ischemic stroke patients and ReN-009 in a Phase I trial in critical limb ischemia.
- **SINUSYS' AerOs** sinus dilation system was granted a CE Mark. It is still under review by the FDA.
- **SUCAMPO PHARMACEUTICALS' Amitiza (lubiprostone)** was approved by the U.K. Medicines and Healthcare products Regulatory Agency to treat adults with chronic constipation not caused by other diseases or treatments.
- **SUREFIRE MEDICAL's Surefire Infusion System** was granted a CE Mark for use in radio- and chemo-embolization procedures.

Regulatory news from other countries

- ***China:*** **VARIAN MEDICAL SYSTEMS' Unique Radiotherapy System** was approved along with the latest release of the **Eclipse** treatment planning software.
- ***Japan:*** **PENUMBRA's Penumbra Coil 400** was approved by the Ministry of Health, Labor, and Welfare to treat brain aneurysms. It will be distributed by **Medico's Hirata**.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
2012		
September 21	**Generic drug user fees**	FDA public meeting
September 21	Classification of posterior **cervical screws**, including pedicle screws	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
September 23	**Regeneron's Eylea** (aflibercept) for central retinal vein occlusion (CRVO)	PDUFA date
September 27-28	Regulatory science considerations for performance validation of **radiation biodosimetry** devices	FDA public meeting
September 28	**Abbott's Humira** (adalimumab) for moderate-to-severe ulcerative colitis	PDUFA date
September 28	**Second Sight's Argus II Retinal Prosthesis System** for severe to profound retinitis pigmentosa	FDA's Ophthalmic Devices Advisory Committee
October 3	Discussion of establishment of a new subcommittee to evaluate the FDA's efforts to address the **challenges in the Science Board's 2007 report**	FDA's Science Board
October 5	Validity, reliability, and usability of **glaucoma imaging devices**	FDA and American Glaucoma Society public workshop
October 12	**Celgene's Abraxane** (nab-paclitaxel) to treat NSCLC	PDUFA date
October 15	Need for and design of **clinical development programs** for approval of **parenteral lipid emulsion products** as nutritional support	FDA's Gastrointestinal Drugs Advisory Committee – ***postponed indefinitely***
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 21	**Impax Laboratories' IPX-066** for Parkinson's disease	PDUFA date
October 24	**Hologic's Selenia Dimensions 3D System –** expanded indication to combine digital breast tomosynthesis with synthetic 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
October 29-31	**Bayer's regorafenib** for metastatic CRC	PDUFA date
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 22	**Medivation** and **Astellas' enzalutamide** (MDV-3100) for castration-resistant prostate cancer	PDUFA date
November 21	**Pfizer's tofacitinib**, an oral JAK inhibitor for rheumatoid arthritis	PDUFA date (extended from August 21)
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 15	**Human Genome Sciences' raxibacumab** to treat anthrax	PDUFA date
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 multidrug-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 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 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 1	**Zogenix's Zohydro** (extended-release hydrocodone) for chronic pain	PDUFA date
April 11	**Sanofi/Genzyme** and **Bayer's Lemtrada** (alemtuzumab) for multiple sclerosis	PDUFA date – delayed because FDA rejected the filing
April 29	**Shire's Vyvanse** (lisdexamfetamine dimesylate), sNDA for ADHD treatment in children	PDUFA date