TRENDS-in-MEDICINE

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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…

Trends-in-Medicine
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SHORT TAKES

- **ADVENTRX PHARMACEUTICALS' Exelbine (vinorelbine injectable emulsion) –** The FDA rejected this non-small cell lung cancer (NSCLC) drug, saying the clinical trials did not substantiate the authenticity of the formulation.
- **Affordable Care Act (ACA) –** The 11th Circuit Court of Appeals ruled that the individual mandate part of the healthcare legislation is unconstitutional. Previously, the 6th Circuit Court of Appeals upheld the individual mandate as constitutional, and that decision was already appealed to the U.S. Supreme Court. The 4th Circuit Court of Appeals in Richmond VA hasn't ruled yet on another challenge to the mandate.
- **ALERE** increased its stake in **Axis-Shield**, an *in vitro* diagnostics tests developer, as part of an unsolicited offer for the company. The deal will be completed if it can buy 90% of Axis-Shield shares.
- **AMARIN's AMR-101 –** The FDA agreed on a special protocol assessment for a six-year "outcomes trial" of this triglyceride-lowering drug derived from fish oil. The company said it plans to submit the drug to the FDA by September 2011.
- **APRICUS BIOSCIENCES' Vitaros (alprostadil) –** The company said it will seek regulatory approval in Mexico, Brazil, Colombia, Argentina, Chile, and Peru for this erectile dysfunction drug.
- **BIOGEN IDEC and ABBOTT's daclizumab –** The companies said a Phase IIb clinical trial of this once-monthly, subcutaneous injectable drug for relapsing-remitting multiple sclerosis had positive results at one year. Patients who received the drug had a 54% lower risk for relapse vs. patients on placebo and met its primary endpoint, but the companies said they have some concerns about side effects and two deaths.
- **BOSTON THERAPEUTICS' metformin –** The company submitted to the FDA an abbreviated new drug application (ANDA) for a chewable version of this Type 2 diabetes drug to compete with **Bristol-Myers Squibb's Glucophage** (metformin) tablets.
- **FOREST LABORATORIES and IRONWOOD PHARMACEUTICALS' linaclotide (guanylate cyclase 2C)** was submitted to the FDA to treat irritable bowel syndrome accompanied by constipation.
- **IMAGING DIAGNOSTIC SYSTEMS' CTLM system –** The FDA gave this breast imaging device a Class III designation requiring premarket approval, concluding it is "not substantially equivalent" to devices cleared through the 510(k) process or to systems categorized as Class I or II devices.

- **Laparoscopic bariatric procedures** – A study in the ***Journal of the American College of Surgeons*** found that procedure volume continued to rise between 2003 and 2008, with the number peaking in 2004 at 135,985 cases, or 63.9 procedures per 100,000 adults, and reaching a plateau in 2008 at 124,838 cases. In-hospital mortality decreased from 0.21% to 0.10% over that time period.

- **MERCK's Temodar (temzolomide), PegIntron (pegylated interferon alfa-2b), and Intron A (interferon alfa-2b)** – Merck was subpoenaed by the Department of Justice (DOJ), which is investigating marketing of these three drugs acquired by Merck with its 2009 acquisition of **Schering-Plough** in what it calls a "federal healthcare investigation." The DOJ is asking for marketing and selling information related to the drugs.

- **RANBAXY LABORATORIES** – The company closed a Gloversville NY plant that produced liquid drug formulations because of "suboptimal" operations. The FDA warned the company about manufacturing violations and stopped approving new products in December 2009.

- **RELIEVANT MEDSYSTEMS' Intracept** – The FDA told the company it can begin a 200-patient pivotal trial of this treatment for chronic axial low back pain, which uses radiofrequency energy delivered through a small access tube into the vertebral body to ablate the basivertebral nerve.

- **WALGREENS** reportedly is planning to sell a variety of health insurance through a private health insurance exchange set up to help people find coverage under the new health reform law. Walgreens already offers basic medical care through in-store clinics.

- **XENOPORT and GLAXOSMITHKLINE's Horizant (gabapentin enacarbil)** – GSK submitted a supplemental new drug application (sNDA) for this restless leg syndrome drug as a therapy for postherpetic neuralgia.

NEWS IN BRIEF

Erythropoiesis-stimulating agents (ESAs) – often misused in cancer patients

A study in the ***Journal of Clinical Oncology*** found cancer patients often improperly receive these anemia drugs, including shorter time periods on the drug than the recommended 2-4 weeks while on chemotherapy, too long on treatment, or treatment when not on chemotherapy. Of the 21,091 patient records analyzed, 24.2% received ESAs for ≤1 week (misuse), and 7.6% received ESAs for >14 weeks (prolonged use). Private-practice physicians and high-volume physicians were less likely to use ESAs for ≤1 week and were more likely to prescribe >24 weeks of treatment. Female oncologists were less likely to prescribe prolonged ESA treatment.

GILEAD SCIENCES

- **AmBisome (amphotericin B).** The company said it fixed the manufacturing quality control problems at its San Dimas CA facility about which the FDA sent a warning letter in September 2010. The violations could have impacted Gilead's ability to export this injectable antifungal drug, but the company said the problems would not have affected tablets made at the plant, including its HIV drugs **Atripla** (efavirenz + tenofovir + emtricitabine) and **Truvada** (emtricitabine + tenofovir).

- **Complera (emtricitabine + tenofovir + rilpivirine).** This combination fixed-dose daily tablet of Gilead's Truvada plus **Johnson & Johnson's Edurant** (rilpivirine) received FDA approval as a stand-alone regimen for treatment naïve HIV adults.

Hip replacements – more negative news for metal

A study in the ***Journal of Bone and Joint Surgery*** (British Volume) found patients getting hip replacements with trabecular metal monoblock components had significantly lower bone mineral density in the surrounding area vs. hip replacement patients with cemented acetabular components. Researchers said during their 55-patient study, "We found that the cemented acetabular component loaded the acetabular bone centromedially whereas the trabecular metal monoblock loaded the lateral rim and behaved like a hemispherical rigid metal component…We suspect that this was due to the peripheral titanium rim used for the mechanism of insertion."

ROCHE/GENENTECH

- **Avastin (bevacizumab).** In a post-FDA advisory committee document, the company suggested Avastin be allowed to keep its indication for metastatic breast cancer but that use be restricted to women with the most aggressive disease and that it be used only with **paclitaxel (Bristol-Myers Squibb's Taxol)**. The company also proposed labeling changes detailing safety and side effects and a medication guide and reiterated its proposal to conduct a new Phase III trial in HER2-negative metastatic breast cancer. The company termed the proposals as "middle-ground."

- **Herceptin (trastuzumab).** A study in the ***Annals of Oncology*** found use of this breast cancer drug in elderly patients increases their risk of heart problems, particularly if

they have a history of heart disease, diabetes, or both. Researchers looked at records of 45 women aged 70-92 treated with Herceptin and found it caused heart problems in 26.7%, a slightly higher rate than seen in early trials in younger and healthier women. Among women with a history of heart disease, 33% developed asymptomatic or symptomatic heart problems after taking the drug vs. 9.1% without a history of heart problems, and 33.3% of women with diabetes developed heart problems vs. 6.1% without diabetes. When the drug was stopped, all but one of the women recovered completely, and five were able to restart treatment.

REGULATORY NEWS

FDA approvals/clearances

- **ABBOTT LABS' RX Herculink Elite** – a renal stent for use in renal artery stenosis patients with uncontrolled high blood pressure.
- **GE HEALTHCARE's Optima CT660** – a compact, low-dose CT imaging system that can be used for cardiac and neurological imaging, among other clinical settings.
- **TOSHIBA's Vantage Titan** – a 3T open-bore magnetic resonance imaging (MRI) scanner with a 71 cm wide semi-open bore and noise-reduction technology.

FDA recalls

The FDA has begun a pilot program to expedite notifications of human drug product recalls by including items in its weekly Enforcement Report about actions that have been determined to be recalls but that remain in the process of being classified as a Class I, II, or III action. This means more items may be included in this list and included sooner. Among the items of potential interest on this week's list were:

- **ADVANCED NEUROMODULATION SYSTEMS' Eon Mini Neurostimulation (IPG) System** – because defective batteries were identified as causing an inability to communicate or recharge the device.
- **AMERICAN MEDICAL SYSTEMS' Elevate System with IntePro Lite**, a prolapse repair system – due to complaints that eyelets were missing from the center graft of some units. No injuries have been reported to AMS so far.
- **GE HEALTHCARE/VITAL SIGNS' cuffable blood pressure cuffs** made in Mexico – because they may not inflate properly due to a leak.
- **LUPIN PHARMACEUTICALS' losartan potassium tablets** – for impurities.
- **NOVARTIS/ALCON/WAVELIGHT's WaveLight FS200 Femtosecond Laser System** – because the software calculating the patterns were found to have a rounding error for certain parameter ranges which could result in an incomplete cut in the donor or patient tissue.
- **NOVARTIS' Fanapt (iloperidone)** – for failed tablet hardness.
- **PFIZER's alprazolam XR tablets** – for failing a dissolution test.
- **SIEMENS MEDICAL SOLUTIONS' Artiste and Oncor linear accelerators** – due to a potential safety risk when certain action buttons are used during the treatment.
- **TEVA:**
  - **Gabapentin tablets** – for contamination with small glass particles.
  - **Lansoprazole delayed-release capsules** – because the color did not meet appearance specification.

European approvals

ALLERGAN's Botox (onabotulinumtoxinA) – The Irish Medicines Board approved this anti-wrinkle injection to treat urinary incontinence associated with spinal cord injury and multiple sclerosis, clearing the way for European approval. In addition, India's drug controller general authorized the drug as prophylactic therapy for chronic migraine.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	August 2011	
August 19	FDA's draft **Strategic Plan for Regulatory Science**, including an update on the Nanotechnology Program	FDA's independent Science Board
August 20	**Regeneron's aflibercept** (VEGF Trap-Eye) for wet AMD	PDUFA date
August 25	**Shire's Firazyr** (icatibant injection) for hereditary angioedema	PDUFA date
August 30	**Seattle Genetics and Takeda's Adcetris** (brentuximab vedotin) for two orphan indications – refractory Hodgkin's lymphoma and anaplastic large cell lymphoma (ALCL)	PDUFA date
	September 2011	
September 7	Design of clinical trials for systemic antibacterial agents for the **treatment of acute otitis media**	FDA public workshop
September 8	**Johnson & Johnson's Xarelto** (rivaroxaban) for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	FDA's Cardiovascular and Renal Drugs Advisory Committee
September 8-9	Safety of **transvaginal mesh** for pelvic organ prolapse	FDA's Obstetrics and Gynecology Devices Advisory Committee
September 9	Safety of **bisphosphonates** in osteoporosis	Joint meeting of the FDA's Reproductive Health Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee
September 13	**Anti-nerve growth factor (NGF)** drug class safety review	FDA's Arthritis Advisory Committee
September 14	**Apotex's Ferriprox** (deferiprone) for transfusional iron overload	FDA's Oncologic Drugs Advisory Committee
	Other 2011 meetings/events	
2H11	**Abbott's RX Acculink** carotid stent	FDA final decision expected
4Q11	**Ophthotech's ARC-1905** primary endpoint results in Phase I trial in dry AMD	Company announcement or medical conference presentation
4Q11	**Roche/Genentech's Lucentis** (ranibizumab) – Phase III HARBOR trial one-year data on the 2 mg dose in wet AMD	Company announcement or medical conference presentation
October 13	**Highly multiplexed microbiology/medical countermeasure (MCM) devices**, for identifying potential disease etiology in situations where many different pathogens share a common clinical manifestation and the simultaneous detection of co-infections	FDA public meeting
October 14	**Gen-Probe's Progensa PCA3 assay** to aid in the decision for repeat biopsy in men age ≥50 with ≥1 previous negative prostate biopsy	FDA's Immunology Devices Advisory Committee
October 17	**Teva Neuroscience's Azilect** (rasagiline mesylate) for a new indication in Parkinson's disease	FDA's Peripheral and Central Nervous System Drugs Advisory Committee
October 28	**Bristol-Myers Squibb and AstraZeneca's dapagliflozin,** the first SGLT-2 for Type 2 diabetes	PDUFA date
October 28	**Pacira Pharmaceuticals' Exparel** (bupivacaine extended-release liposome injection), a painkiller	PDUFA date
December	**Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to complete	Company announcement or medical conference presentation
December 8	**Antares Pharma's Anturol** (transdermal oxybutynin ATD gel), a treatment for overactive bladder	PDUFA date
December 13	**Endo Pharmaceuticals' Opana** (extended-release oxymorphone), a painkiller	PDUFA date
	2012 meetings/events	
January	**Pfizer's Prevnar 13** (PCV13), a pneumococcal vaccine for adults	PDUFA date
January 28	**Eli Lilly, Amylin Pharmaceuticals and Alkermes' Bydureon (weekly exenatide XR)**, an injectable drug for Type 2 diabetes	FDA decision date
February	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation
February 17	**Corcept Therapeutics' Corlux** (mifepristone) for Cushing's syndrome	PDUFA date
February 28	**Pfizer's axitinib** for advanced renal cell carcinoma	PDUFA date (*approximate*)
March 27	**Affymax and Takeda's peginesatide** for anemia	PDUFA date
April 30	**Vivus' avanafil** for erectile dysfunction	PDUFA date (*approximate*)
April 30	**Baxter and Halozyme's HyQ** for immunodeficiency	PDUFA date