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…

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SHORT TAKES

- **4SC AG's resminostat** met the primary endpoint in a 33-patient Phase II clinical trial in patients with relapsed/refractory Hodgkin's lymphoma. The company said the drug showed anti-tumor activity in 11 patients. The drug also is being tested in liver cancer and colorectal cancer.
- **ARDEA BIOSCIENCES' lesinurad** – The FDA and the company have agreed on the design of a Phase III trial for this gout drug.
- **BAUSCH + LOMB** has decided it wants a femtosecond of its own, so it has taken an option to buy **Technolas Perfect Vision**, which manufactures femtosecond laser technology. Technolas was established in 2009 as a joint venture between B+L and **20/10 Perfect Vision**.
- **BIOGEN IDEC** is taking full control of its joint ventures in Italy and Switzerland, ending a partnership with Italian drugmaker **Dompé Group** on the marketing of two multiple sclerosis drugs, **Avonex** (interferon beta-1a) and **Tysabri** (natalizumab).
- **CLAL BIOTECHNOLOGY INDUSTRIES and CURETECH's CT-011** – A Phase II trial in lymphoma had positive results.
- **DISCOVERY LABORATORIES' Surfaxin (lucinactant)** – The company said it responded to the FDA's 2009 letter outlining the Agency's concerns about this preventive therapy for respiratory distress syndrome in premature infants. Discovery expects a six-month review period.
- **ENDOLOGIX' Ventana** – The company got a conditional Investigational Device Exemption (IDE) to start clinical studies of this stent graft for renal aortic aneurysms, designed for use with the company's Xpand renal stent grafts and AFX endovascular system.
- **EXELIXIS' cabozantinib** – The company said the pre-specified number of progression-free survival (PFS) events required for unblinding of the data in its ongoing Phase III pivotal trial (EXAM) of cabozantinib in patients with medullary thyroid cancer (MTC) has been reached, and top line data are expected to be released in 4Q11. Cabozantinib is being developed under a Special Protocol Assessment (SPA) with the FDA that allows for full approval on the basis of PFS data.
- **GENZYME's Fabrazyme (agalsidase beta)** – The company said it was unable to distribute last month's supply on time because of "an unexpected delay related to our quality release process." Apologizing to patients for the delay, the company said it expects to provide the August shipment this month.

- **MEDICIS PHARMACEUTICALS' LipoSonix**, an ultrasound device to remove fat deposits around the stomach, was cleared by the FDA, but the company does not plan to launch it in the U.S. Instead, Medicis wants to sell that business unit.
- **NANOVIRICIDES' NV-INF-1** – The company plans to submit this flu drug to the FDA soon as high-dose therapy for hospital patients and as a single-course treatment for outpatients.
- **PAR PHARMACEUTICALS COMPANIES, ALPHAPHARM, and GENPHARM** are being sued by a whistleblower who has accused the companies of scheming to overcharge the government by tens of millions of dollars for their drugs. Assistant U.S. Attorney Linda Wawzenski of Chicago has joined in the case but only against Par.
- **PFIZER's tofacitinib** – Abstracts released in advance of the American College of Rheumatology meeting in November indicate this JAK2 inhibitor, an oral rheumatoid arthritis therapy, is as effective as **Abbott's Humira** (adalimumab). But there are still safety concerns, including elevated creatinine and LDL and decreased hemoglobin.
- **Psychiatric drugs** – In a cost-cutting move, the Illinois Department of Healthcare and Family Services has cut access for Medicaid patients to 17 brand-name psychiatric drugs, saying there are cheaper alternatives. *Will other states follow suit?*
- **TEVA PHARMACEUTICAL INDUSTRIES and ALCOBRA's MG01Cl**, a drug for attention-deficit/hyperactivity disorder (ADHD), met the primary endpoints in a Phase II trial, with 56% of MG01Cl patients vs. 36% of placebo patients having a reduction in symptoms of ≥25%. In addition, 44% of MG01Cl patients vs. 25% of placebo patients improved ≥40%.
- **VERTEX PHARMACEUTICALS' VX-509**, at the two highest doses, met the endpoints in a 204-patient Phase II trial in refractory rheumatoid arthritis. Side effects included nausea, headache, and elevated liver enzymes.

NEWS IN BRIEF

Automated external defibrillators (AEDs) – failures common

A retrospective study published in the ***Annals of Emergency Medicine*** found the FDA received >1,000 reports over 15 years of deaths following failure of AEDs. In 37 of the events, the defibrillator failed to even power on, and in 22% of the cases the device was unable to complete the heart rhythm analysis. The most common failure, which occurred in 45% of cases, was failure to deliver a shock. The researchers recommended public access programs provide backup units when possible.

Bisphosphonates – panel recommends FDA strengthen warnings

The FDA's Reproductive Health Drugs Advisory Committee, meeting jointly with the FDA's Drug Safety and Risk Management Advisory Committee, voted 17 to 6 that the duration of use for these drugs to treat osteoporosis should be clarified, but they didn't say what the duration of use should be. The panel was concerned about safety issues that have arisen since approval, particularly atypical fractures, osteo-necrosis of the jaw (ONJ), and perhaps esophageal cancer and told the FDA additional studies are warranted and doctors and patients should regularly review continued use. While the panel did not recommend a specific time limit on therapy, use >5 years is questionable except perhaps in the most high-risk patients.

BOSTON SCIENTIFIC's Wingspan – not beneficial, raising questions about stenting

A study by researchers at the Medical University of South Carolina, published in the ***New England Journal of Medicine***, found aggressive medical therapy was more than twice as effective in lowering the risk of recurrent stroke or death than stenting of narrowed intracranial arteries. In the randomized SAMMPRIS trial, 14.7% of patients getting percutaneous transluminal angioplasty and stenting (PTAS) developed fatal or non-fatal strokes at 30 days (the primary endpoint) vs. 5.8% of patients in the aggressive medical management group (p=0.002).

One-year death/stroke was also significantly lower with medical management (12.2% vs. 20% with stenting). The 451-patient SAMMPRIS trial was stopped early because of the significant stroke and mortality rate in the stent arm.

Wingspan was approved by the FDA in 2005, and other stents have been approved since then with this as the predicate device, raising questions about both the efficacy/safety of those devices and the FDA approval process.

BRONCUS TECHNOLOGIES' Airway Bypass – fails pivotal trial

The pivotal Phase III EASE trial failed, showing no sustained benefit for this airway stent, an alternative to surgical lung volume-reduction surgery, in improving lung function in patients with severe emphysema over a sham procedure. Airway Bypass did release trapped gas from hyperinflated

regions on Day 1, but the benefit was not sustained at 3, 6, or 12 months.

GLAXOSMITHKLINE

- **GSK-052.** GSK got a contract from the Department of Health and Human Services' (HHS's) Biomedical Advanced Research and Development Authority to develop this antibiotic, which it licensed from **Anacor Pharmaceuticals**, for intra-abdominal infection and ventilator-associated pneumonia.
- **Cervarix (HPV vaccine).** A 7,500-patient study conducted in Costa Rica by U.S. National Cancer Institute researchers and published in the ***Journal of the National Cancer Institute*** found two doses of this vaccine against human papillomavirus (HPV) appeared just as effective as the recommended three-dose regimen.
- **Tykerb (lapatinib).** GSK stopped the head-to-head monotherapy arm of the >8,000-patient ALTTO breast cancer trial of Tykerb and Roche/Genentech's Herceptin (trastuzumab) after an interim analysis showed Tykerb had lower efficacy than Herceptin and was unlikely to meet the pre-specified non-inferiority goal on disease-free survival. Three other arms of the trial will continue uninterrupted: a Herceptin monotherapy arm and two arms that sequence Tykerb and Herceptin in different order.

JOHNSON & JOHNSON's Xarelto (rivaroxaban) –positive FDA panel but could be delayed

The FDA's Cardiovascular and Renal Drugs Advisory Committee voted 9-2, with one abstention, to recommend the FDA approve this direct oral factor Xa inhibitor to prevent stroke in patients with non-valvular atrial fibrillation. However, several panel members said at least a short study of transitioning patients to warfarin should be done prior to approval, the panel did not support a superiority claim, and some members said it should be labeled as second- or third-line therapy.

NSAIDs – linked to miscarriages

A Canadian study published in the ***Canadian Medical Association Journal*** found some non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of miscarriage when taken in the first 20 weeks of a pregnancy. University of Montreal researchers compared 4,700 women who had a miscarriage to 47,000 who did not and found women who had miscarriages in the first 20 weeks of their pregnancy were more than twice as likely to have taken an NSAID.

- Diclofenac tripled the risk.
- Naproxen showed a 2.64-fold increase in risk.
- Ibuprofen doubled the risk.

QIAGEN and LILLY – partnering on JAK2 inhibitor

Qiagen has partnered with Lilly on the development, manufacturing, and commercialization of a molecular diagnostic for JAK2 V617F as a qualitative and quantitative companion test for Lilly's JAK2 inhibitor, which is in Phase I development. The assay is intended to identify patients most likely to benefit from treatment with JAK2 inhibitors, and it will be used during Lilly's clinical trials. Qiagen said it gained exclusive access to the JAK2 biomarker through an agreement with **Ipsogen**, a French company it is acquiring.

ROCHE

- **Actemra (tocilizumab).** A study published in ***The Lancet*** suggested this rheumatoid arthritis drug may have utility in asthma by reducing airway inflammation.
- **Avastin (bevacizumab).** A report by HHS's Office of the Inspector General found Medicare could have saved a billion dollars – and Medicare patients could have saved another $275 million – over two years if ophthalmologists had prescribed Avastin instead of **Roche/Genentech's Lucentis** (ranibizumab) for wet age-related macular degeneration. The report also urged the Centers for Medicare and Medicaid Services (CMS) to ask Congress for more power to demand lower costs from manufacturers of expensive biologic drugs like Lucentis.
- **EVT-302.** Roche is buying the rights from **Evotec AG** to this drug intended to treat Alzheimer's disease by targeting monoamine oxidase type B (MAO-B), an enzyme that breaks down dopamine in the brain and contributes to the production of free radicals, which may contribute to the spread of the disease.

Transvaginal mesh – FDA panel recommends stricter testing, surveillance

The FDA's Obstetrics and Gynecology Devices advisory panel agreed with the FDA's proposal for stringent premarket testing of vaginal mesh products for the treatment of pelvic organ prolapse (POP) and stress urinary incontinence (SUI). The panel agreed transvaginal mesh for POP should be reclassified from Class II to Class III in light of safety concerns and lack of significant clinical benefit. This means manufacturers will have to prove the devices are safe and effective, that they can't use existing devices as predicates, and a premarket clinical trial must be conducted.

The panel also recommended that existing mesh products for SUI repair do not have to be reclassified because the adverse events are not as great as with POP. However, new products must conduct premarket studies, most likely randomized controlled studies. The panel agreed postmarket surveillance studies should not be required for SUI.

As for the newer, so-called mini-slings for SUI repair, all but one panel member agreed there is not enough safety and effectiveness data, and premarket trials need to be conducted. The panel also recommended postmarket studies for currently marketed mini-slings, either randomized controlled trials or cohort studies.

Tumor Necrosis Factor-alpha (TNFα) inhibitors

- **Boxed warning.** The FDA updated the boxed warning on the labels of all drugs in this class to add a warning that they increase the risk of infection from two bacterial pathogens, Legionella and Listeria. The labels for these drugs – which are used to treat rheumatoid arthritis, Crohn's disease, ulcerative colitis, and psoriasis – also were revised to include more consistent information about the risk for serious infections and the associated disease-causing pathogens.
- **Skin cancer.** A review by French researchers, published in the ***Annals of Rheumatic Diseases***, of 29 earlier studies of TNF inhibitors concluded the drugs increase the risk of skin cancer, though they do not appear to increase the risk of other cancers.

REGULATORY NEWS

FDA budget may not be as bad as expected

The Senate Appropriations Committee reportedly plans to propose increasing the FDA budget by $50 million for FY2012, although the House reportedly is looking to cut the FDA budget by $285 million.

FDA training for medical device reviewers

The FDA announced two new training programs designed to improve the consistency of medical device reviews by enhancing the skills of the people reviewing premarket applications (PMAs) at the Center for Devices and Radiological Health (CDRH). The program includes ≤18 months of training. CDRH also is developing a pilot Experiential Learning Program for premarket reviewers that will begin in 2012 and will include visits to academic institutions, manufacturers, research organizations, and healthcare facilities.

European regulatory actions

- **ASCENDX SPINE's Ascendx VCF Repair System** received a CE Mark to treat vertebral compression fractures. The company was formerly known as AOI Medical.
- **HEMOSPHERE's HeRO Graft vascular access device** received a CE Mark as an alternative to central venous catheters in hemodialysis patients.
- **JOHNSON & JOHNSON's Zytiga (abiraterone)**, a once-daily oral treatment for chemotherapy-refractory prostate cancer, was approved.
- **MELA SCIENCES' MelaFind**, a hand-held, computer-assisted device to help dermatologists more accurately diagnose melanoma, was approved. The company plans to start marketing in Germany first. The FDA has not yet approved it.
- **ST. JUDE MEDICAL's Genesis**, an implantable device to treat chronic migraines, was approved.
- **VIROPHARMA's Buccolam (liquid midazolam)** was approved to treat epileptic seizures in infants, toddlers, and children <age 18.

FDA approvals/clearances

- **SAGENT PHARMACEUTICALS' injectable haloperidol** was approved, and the company plans to launch it in 4Q11 to treat schizophrenia and Tourette syndrome.
- **SHIRE's Vyvanse (lisdexamfetamine)** – The FDA approved a supplemental NDA for use of this hyperactivity drug to treat dermatillomania, also known as compulsive skin picking or CSP.

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

- **AMGEN's Vectibix (panitumumab)** was rejected for metastatic colorectal cancer, even though it was found to have a survival benefit, because it failed to show cost-effectiveness.
- **MERCK KGAA's Erbitux (cetuximab)** was rejected for metastatic colorectal cancer, even though NICE said it prolonged life after other drugs failed, because it failed to show cost-effectiveness.
- **MERCK/NYCOMED's Daxas/Daliresp (roflumilast)** needs another clinical trial before NICE will recommend it to treat patients with chronic obstructive pulmonary disease (COPD). NICE said there is too much uncertainty as to its value as an add-on to other treatments.

- **ROCHE**
  - **Avastin (bevacizumab)** was rejected for metastatic colorectal cancer. NICE found "no evidence" that it prolonged survival in these patients.
  - **MabThera (rituximab)** was approved in combination with more chemotherapy regimens to treat advanced follicular lymphoma.

TAKEDA PHARMACEUTICAL's Mepact (mifamurtide) was approved for use with chemotherapy after surgery for non-metastatic bone cancers. NICE rejected the drug last year, but the company cut the price, and a new cost-effectiveness analysis was positive.

FDA recalls

- **ABBOTT LABORATORIES' Nimbex (cisatracurium besylate) injection** – due to the presence of one foreign Lyo-stopper on one single vial discovered during visual inspection of a subsequently manufactured and undistributed lot.
- **ASTRAZENECA's Vimovo (naproxen/esomeprazole magnesium)** – because of failing dissolution tests.
- **BRISTOL-MYERS SQUIBB's Coumadin (warfarin)** – because some tablets may not meet potency specifications.
- **ENDO PHARMACEUTICALS' Endocet (oxycodone and acetaminophen)** – because of adulteration.
- **INTUITIVE SURGICAL's da Vinci Surgical System** – for potential failure of the retention component of the master tool manipulator.
- **MEDTRONIC's SynchroMed II, Model 8637 pump** – because of the potential for reduced battery performance.
- **PHARMACEUTICAL ASSOCIATES' Mag-Al Plus antacid** – because blue plastic particles were detected in unscreened lots.
- **TELEFLEX MEDICAL's urinary tract catheters** – because pin holes were detected and sterility cannot be guaranteed.
- **TEVA PHARMACEUTICALS' fluconazole** – because there is a chance that the 200 mg tablets may be mixed in bottles of product labeled 100 mg.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	September 2011	
September 12-13	**Proposed regulation of mobile health applications**	FDA workshop
September 13	**Anti-nerve growth factor (NGF)** drug class safety review	FDA's Arthritis Advisory Committee – postponed indefinitely
September 14	**Apotex's Ferriprox** (deferiprone) for transfusional iron overload	FDA's Oncologic Drugs Advisory Committee
September 16	Institute of Medicine's recommendations on replacing the **FDA's 510(k) clearance program** for medical devices	FDA public meeting
September 20	**Overview of the research program** in the Laboratory of Enteric and Sexually Transmitted Diseases, Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and Review, CBER, FDA	FDA's Vaccines and Related Biological Products Advisory Committee meeting at NIH ***via teleconference***
September 26	**Drug shortages**	FDA public workshop
September 26-27	**Tissue adhesive materials**	FDA workshop on facilitating innovation in these products
September 30	Institute of Medicine's recommendations for FDA's reform of the **510(k) device clearance program**	Public comment deadline
	October 2011	
October 12	**FDA guidance on diagnostic tests** being developed simultaneously with a drug/biologic	New deadline for industry comment
October 13	**Highly multiplexed microbiology/medical countermeasure (MCM) devices,** for identifying potential disease etiology	FDA public meeting
October 14	**GenProbe's Progensa PCA3 assay** to aid in the decision for repeat biopsyin men age ≥50 with ≥1 previous negative prostate biopsy	FDA's Immunology Devices Advisory Committee – ***postponed***
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 ER), a painkiller	PDUFA date
	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
November 5	**Johnson & Johnson's Xarelto** (rivaroxaban) for stroke prevention in AFib	PDUFA date
November 18	**Regeneron's Eylea** (aflibercept, VEGF Trap-Eye) for wet AMD	New PDUFA date
December	**Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to be completed	Company announcement or medical conference presentation
December 8	**Antares Pharma's Anturol** (transdermal oxybutynin ATD gel), for overactive bladder	PDUFA date
December 13	**Endo Pharmaceuticals' Opana** (extended-release oxymorphone), a painkiller	PDUFA date
	2012	
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 26	**Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in prostate cancer	PDUFA date
April 27	**Salix Pharmaceuticals and Progenics Pharmaceuticals' Relistor** (methylnaltrexone injection) for opioid-induced constipation	PDUFA date
April 29	**Vivus' avanafil** for erectile dysfunction	PDUFA date
April 30	**Baxter and Halozyme's HyQ** for immunodeficiency	PDUFA date