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

- **AFFYMAX and TAKEDA PHARMACEUTICAL's peginesatide,** an anti-anemia drug, was submitted to the FDA to treat anemia in patients with chronic kidney failure who are on dialysis.
- **ALEXION PHARMACEUTICALS' Soliris (eculizumab)**, a complement inhibitor, was granted accelerated review by the FDA as a treatment for atypical hemolytic uremic syndrome (aHUS). The company also submitted the drug to European regulators. It is already approved in the U.S. to treat paroxysmal nocturnal hemoglobinuria.
- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran)**, an oral thrombin inhibitor, received preferred Tier 2 formulary status with all AARP Medicare Part D plans.
- **BOSTON SCIENTIFIC's iCross coronary imaging catheters** were recalled after eight confirmed instances where the device came off during an implant procedure.
- **BRISTOL-MYERS SQUIBB's Yervoy (ipilimumab) and ROCHE's vemurafenib –** The companies are teaming up for a combination study of these two treatments for metastatic melanoma, the first an immune modulator and the other a BRAF inhibitor.
- **ERCHONIA's Zerona MLS –** The FDA sent the company a warning letter after finding it was advertising this laser scanner for use in liposuction and body contouring for other indications – e.g., Parkinson's disease, to reduce LDL and low-density lipoprotein (LOL), and to suppress appetite.
- **Flu vaccines –** In a study published in the journal ***Science Translational Medicine***, researchers reported progress with a flu vaccine using an oil-in-water adjuvant, MF59, which would allow faster scale-up in a pandemic. The method, which already is in use in Europe, requires only half the current amount of antigen to produce the avian and swine flu vaccines.
- **German drug prices –** A new drug pricing law in Germany means pharmas now will have to show their drug is not only safe and more effective than placebo but also worth more than older therapies. If a pharma can't convince German regulators that its agent is more efficacious or has additional benefits, then it cannot charge more than existing medications already on the market.
- **GLAXOSMITHKLINE and THERAVANCE's Relovair (fluticasone/vilanterol) –** The companies reported positive results from two six-month Phase III studies of this respiratory disorder drug in patients with chronic lung disease. The Relovair patients had superior lung capacity vs. patients taking placebo. Twelve-month studies are under way.

- **PFIZER's axitinib**, a small molecule tyrosine kinase inhibitor, was submitted to European regulators to treat advanced renal cell carcinoma in patients refractory to other therapies.
- **REGEN BIOLOGICS' Menaflex** – The company sued the FDA for rescinding the approval of this knee implant and removing it from the market after determining the device should never have been approved in the first place.
- **TERUMO AMERICAS HOLDING** is acquiring **Harvest Technologies**, a biotechnology developer of point-of-care devices that allow physicians to derive autologous adult stem cells from their patients.
- **TIOGA PHARMACEUTICALS' asimadoline**, a kappa opioid receptor agonist, was granted fast track status for the treatment of irritable bowel syndrome (IBS) with diarrhea.
- **YM BIOSCIENCES' CYT-387**, a JAK inhibitor for myelofibrosis, was granted orphan drug status by European regulators. The FDA had already granted orphan drug status.

NEWS IN BRIEF

Angiotensin receptor blockers (ARBs) – no cancer risk

After reviewing 31 randomized clinical trials with >155,000 patients, the FDA found these high blood pressure medications do not increase the risk of developing cancer. The FDA began its review of the safety of ARBs in July 2010 after a study found a small increased risk of cancer in patients taking an ARB.

ASTRAZENECA

- **Brilinta/Brilique (ticagrelor)**, a blood thinner, was approved by Health Canada for secondary prevention of atherosclerotic events in patients with acute coronary syndrome (ACS). The newest FDA PDUFA date is July 20, 2011.
- **Conferences** – AstraZeneca will no longer fund physician attendance at overseas medical conferences and will, instead, focus on "local educational opportunities." The change comes at a time when the company's financial relationships with the medical community are under scrutiny. The question is whether other pharmas will follow suit and what that will mean for attendance at conferences.

Banning drug ads – wouldn't lower drug prices

The Congressional Budget Office (CBO) said in a report that proposed bans or reductions of prescription drug advertising aimed at consumers would not do much to lower prices. The CBO said pharmas wouldn't lower drug prices but would shift their ad dollars to physician marketing.

BAYER's oral contraceptives – warning about clots

The FDA issued a warning that birth control pills containing drospirenone – e.g., Bayer's Yaz, Yasmin, Safyral, and Beyaz – may increase the risk of blood clots. The FDA cited two newly published studies that evaluated the risk of venous thromboembolism (VTE) in women who use drospirenone-containing birth control pills to those containing a different progestin, levonorgestrel. They found a 2- to 3-fold increased risk of VTE with the drospirenone-containing pills. However, other studies have not reported an increased risk, so the FDA is evaluating the conflicting results and will make its findings public when that analysis is completed.

Genetic tests – studies criticize DTC services

Two studies presented at the European Society of Human Genetics meeting in Amsterdam were critical of direct-to-consumer (DTC) genetic tests.

- Belgian researchers surveyed clinical geneticists from 28 European countries on their experience with and attitudes toward DTC genetic testing. They found:
  - 69% of respondents felt prenatal gender tests should be legally banned.
  - 63% wanted to ban whole genome scans by DTC companies.
  - 90% said a test that purports to predict if an asymptomatic person has a very high probability of developing a condition should not be allowed without face-to-face medical supervision.
- Dutch researchers studied the predictive ability of tests by deCODEme and 23andMe(USA) in eight common multifactorial diseases – age-related macular degeneration (AMD), atrial fibrillation, celiac disease, Crohn's disease, heart attack, prostate cancer, and Type 1 and Type 2 diabetes. They found the predictive ability of the tests was "moderate" for all diseases. However, they found both companies assigned an increased risk to a substantial number of testers, even though their risk often was not substantially higher than in the general population.

Gp100 vaccine – enhances IL-2 in advanced melanoma

A randomized, 185-patient Phase III trial published in the ***New England Journal of Medicine*** found a GP100 peptide vaccine significantly enhanced the response to interleukin-2 (IL-2) and slowed disease progression in patients with advanced melanoma.

The researchers reported:

- A response in 16% of vaccine/IL-2 patients vs. 6% of IL-2 patients (p=0.03).
- Significantly longer PFS with vaccine: 2.2 months vs. 1.6 months (p=0.008).
- Median overall survival of 17.8 months with vaccine vs. 11.1 months for IL-2 (Nss).
- Vaccine-related adverse events included transient, reversible sinus tachycardia and supraventricular arrhythmia.

Interestingly, when a GP100 peptide vaccine was combined with **Bristol-Myers Squibb's Yervoy** (ipilimumab), the biologic alone had better results, and the researchers said it is not clear why this trial had a different result.

MRSA in hospitalized patients – probably of animal origin

A new type of methicillin-resistant *Staphylococcus aureus* (MRSA) that is not detected by traditional genetic screening methods was discovered in Irish hospitals, according to a report in the journal ***Antimicrobial Agents and Chemotherapy***. The Irish researchers identified the new MRSA strain using high throughput DNA microarray screening and suggested it may have come from cattle. Complete genome sequencing revealed this strain is distinctly different from previously described MRSA.

Pharmacy computer software – not protecting patients from drug-drug interactions

A study published in the ***Journal of the American Pharmacists Association*** found pharmacy computer systems aren't doing the job they are expected to do – protect against harmful drug interactions by flagging potentially dangerous combinations before a prescription is filled. The study, which examined 64 Arizona pharmacies (chain, independent, and hospital), found the computer systems are flawed. Only 28% of pharmacies tested with a list of 13 potentially dangerous drug interactions got a perfect score.

Thermography – not the same as mammography

The FDA warned doctors and patients that thermography is not a substitute for a mammogram in breast cancer detection. Infrared thermography devices are cleared by the FDA for use as an adjunct tool, but they should not be used to screen for or diagnose breast cancer.

The FDA sent warning letters to healthcare providers who have been promoting the inappropriate use of breast thermography, and the Agency sent a warning letter to an unnamed thermography manufacturer that claimed thermal imaging could take the place of mammography. The FDA said it is unaware of any valid scientific evidence showing thermography, used alone, is effective for breast cancer screening.

REGULATORY NEWS

Accountable care organizations (ACOs) – Republican senators express concern

Seven Republican senators – all members of the Senate Finance Committee – wrote Department of Health and Human Services (HHS) Secretary Kathleen Sebelius and Centers for Medicare and Medicaid Services (CMS) Administrator Donald Berwick, MD, expressing concern about the regulation of ACOs and warning they will be a failure and will have not achieved the intended purposes. They said, "We have been struck by the increasingly diverse chorus of concerns many of our nation's leading healthcare institutions have raised in recent days about the proposed ACO regulation."

The senators cited concerns expressed by:

- Integrated health providers such as Intermountain Healthcare and the Cleveland Clinic.
- All 10 members of the Physician Group Practice (PGP) CMS demonstration project.
- Providers who said incentives and accountability are misaligned.

The senators asked HHS and CMS to withdraw the proposed rule and craft a new rule with input from stakeholders.

CMS gets flexible on e-prescribing – more exemptions available

CMS announced it will be more flexible in allowing doctors to phase in electronic prescribing technology. Currently, doctors can qualify for an additional 1% in Medicare Part B payments in 2011 and 2012 plus a 0.5% increase in 2013 by using a certified e-prescribing system. However, doctors who don't do at least 10 e-prescriptions with a qualified system in the first

half of this year will see their Medicare reimbursements cut by 1% in 2012, 1.5% in 2013, and 2% in 2014.

The new rule expands the number of doctors who are exempt from the incentive and the penalty, but the exemptions are still fairly restricted. Rural physicians without adequate high-speed Internet access were already exempt, but new reasons include limited prescribing activity in the past six months or living where regulations hinder e-prescribing (e.g., where narcotics are not allowed to be e-prescribed). CMS advises these doctors to apply for "hardship exemption" before October 1, 2011.

CMS is accepting public comments on the proposed rule until July 25, 2011.

Congressional investigation of FDA expanded – over 2008 heparin issue

House Republicans have expanded their investigation into how the FDA handled the 2008 contamination of heparin from China and are asking for documents from U.S. Immigration and Customs Enforcement. The legislators said they are frustrated with the FDA's unresponsiveness to their questions, so they are seeking answers from other government agencies. They also complained the FDA is not pursuing the root cause of the contamination, does not know the source of the original contamination, and did not inspect Chinese plants making ingredients for the drug.

Electronic medical records (EMRs) – mixed impact on errors

A study in the ***Journal of General Internal Medicine*** found changing to EMRs reduces prescribing errors overall but certain types of errors increase in the short term. Investigators followed 17 physicians at an outpatient clinic that switched to a newer EMR system. Overall, they found prescribing errors fell from 35.7 errors per 100 prescriptions to 21.1 at 12 weeks and 12.2 at one year. However, mistakes in directions and frequency were higher at 12 weeks than before the new EMR system was implemented. And the rates of some errors were higher even after 12 months of the new system.

PFIZER's Chantix (varenicline) – adverse event reporting irregularities

An analysis by the non-profit Institute for Safe Medication Practices charged that hundreds of suicides, psychotic reactions, and other serious problems related to this smoking cessation drug were left out of an FDA safety review because Pfizer submitted data through "improper channels." The analysis found ~150 additional suicides, nearly doubling the total. The FDA asked Pfizer to resubmit thousands of records after realizing the company was sending the required reports in a format that could not be entered into the FDA's Adverse Events Reporting System (AERS). However, the FDA said Pfizer is now in compliance with reporting requirements.

European regulatory approvals

- **CROMA PHARMA and BAUSCH + LOMB's Yellox (bromfenac sodium sesquihydrate)** – an NSAID eye drop for postoperative ocular inflammation.
- **SECOND SIGHT's Argus II**, an artificial retina that restores sight in people blinded by retinitis pigmentosa – by sending signals from a camera worn on glasses to the optic nerve – was approved following testing in 30 patients.
- **STAAR SURGICAL's KS-SP** Preloaded Single Piece Hydrophobic Acrylic Intraocular Lens.

Recent FDA approvals/clearances

- **COVIDIEN's Parietex Optimized Composite (PCOx)**, a mesh used in surgical hernia repair, received 510(k) clearance as well as approval from European regulators. The company plans to start selling it this month.
- **SOPHONO's Otomag Alpha 1 Bone Conduction Hearing System** – an implantable hearing aid that uses magnetic coupling.
- **THERMOGENESIS' Res-Q** – a system to process stem cells from bone marrow to prepare platelet-rich plasma.

Recent FDA recalls

- **APOGEE MEDICAL's perindopril erbumine** – This antihypertensive failed stability testing at 12 months.
- **DEFIBTECH's Lifeline AED and ReviveR AED** – because they may not shock during the charging process.
- **JOHNSON & JOHNSON/DEPUY's Mitek Gryphon anchors** – because of metal debris in the shaft component.
- **JOHNSON & JOHNSON/MCNEIL's Sudafed (pseudoephedrine HCl)** – This nasal decongestant was recalled because of a typographical error on the carton.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	June 2011	
June 8-9	**Reprocessing medical devices**	FDA public workshop
June 17	**Regeneron Pharmaceuticals' aflibercept** (VEGF Trap-Eye) for wet AMD	FDA's Dermatologic and Ophthalmic Drugs Advisory Committee
June 17	**Celgene's Istodax** (romidepsin) – sDNA for peripheral T-cell lymphoma	PDUFA date
June 17	**Pfizer/King Pharmaceuticals' Acurox** (immediate-release oxycodone), a painkiller	PDUFA date
June 20	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	Company to meet with FDA on complete response letter
June 21	**Novartis's Ilaris** (canakinumab) for the treatment of gouty arthritis attacks	FDA's Arthritis Advisory Committee
June 23	**Shire's Firazyr** (icatibant injection) for hereditary angioedema	FDA's Pulmonary-Allergy Drugs Advisory Committee
June 23	**Pfizer/King Pharmaceuticals/Pain Therapeutics' Remoxy** (tamper-resistant oxycodone CR) for pain	PDUFA date
June 23-24	**HCV drug development**	Workshop on Clinical Pharmacology of Hepatitis Therapy, Boston
June 28-29	**Roche/Genentech's Avastin** (bevacizumab), hearing on appeal of FDA's decision to withdraw the indication for metastatic breast cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
June 29	**Cellular and gene therapy products** for retinal disorders	FDA's Cellular Tissue and Gene Therapies Advisory Committee
	Other 2011 meetings/events	
July 11	**Novartis's Arcapta Neohaler** (indacaterol) long-acting beta agonist (LABA) for COPD	PDUFA date
July 20	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
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 brentuximab vedotin** for two orphan indications – refractory Hodgkin's lymphoma and anaplastic large cell lymphoma (ALCL)	PDUFA date
2H11	**Abbott's RX Acculink** carotid stent	FDA final decision expected
Summer	Report on **FDA 510(k) reform**	Institute of Medicine
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
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 Gel** (oxybutinin gel), a treatment for overactive bladder	PDUFA date
	2012 meetings/events	
February 2012	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation