TRENDS-in-MEDICINE

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Quick Takes

…Highlights from this week's news affecting drugs and devices in development that are not covered in longer *Trends-in-Medicine* reports…

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SHORT TAKES

- **ABBOTT's glucose test strips** – The FDA issued a Class I recall on six brands of Abbott's diabetes test strips, saying they could give inaccurate results. The company voluntarily pulled them all from the market.

- **ADVENTRX PHARMACEUTICALS' ANX-514**, an emulsion version of **Sanofi-Aventis**'s Taxotere (docetaxel), was rejected by the FDA, which said it must undergo further testing before approval to determine if the reformulation is biologically equivalent to the original product. In a 10-month bioequivalence study conducted in 2008/2009, the reformulation was as safe as docetaxel, but higher amounts of the new version of the drug were found in the blood of patients during and immediately after treatment.

- **ALKERMES' ALKS-37** – Alkermes announced that the top-line results from an 87-patient trial in patients with chronic non-cancer pain showed that ALKS-37 significantly relieved opioid-induced constipation without reducing the effectiveness of the opioid. The company reported that patients on the two highest doses of ALKS-37 (30 mg/day and 100 mg/day) had a significant increase in the number of bowel movements per week vs. placebo. The most common side effects were abdominal pain and diarrhea. A Phase III trial is expected to start by mid-2011.

- **ALLERGAN's Lap-Band** received an expanded indication from the FDA to somewhat less obese individuals. Now, in addition to patients with a body mass index ≥40, it can be used in adults with an obesity-related condition who have a BMI ≥30 (instead of the previous 35).

- **ASTELLAS PHARMA** is buying the rights to **Aveo Pharmaceuticals**' tivozanib, an experimental treatment for renal cell carcinoma that is in Phase III development. Outside North America and Europe, Astellas will handle all development and marketing.

- **BIOPTIGEN** – The FDA sent the company a warning letter, saying the company has been promoting its hand-held eye imaging scanner for diagnostic purposes (e.g., retinopathy of prematurity and pediatric retinoblastoma) that have not been cleared by the Agency. The FDA also said modifications had been made to the optical coherence tomography (OCT) device that were not part of the 510(k) clearance.

- **BIOSANTE PHARMACEUTICALS' LibiGel** – The company reported that a Phase III study in 2,869 women found this topical testosterone gel boosts the sex drive of women.

- **CEPHALON's Fentora (fentanyl buccal)** – The U.S. Postal Service's Office of the Inspector General subpoenaed Cephalon, seeking information on this drug for cancer pain. Reportedly, the investigation is in connection with an investigation related to workers' compensation claims by Postal Service employees.

- **Fibrates** – There is a rumor that the FDA's Cardiovascular and Renal Drugs Advisory Committee will meet in May 2011 to review data on fibrates, including the ACCORD and FIELD trials as well as other data, but no official date has been announced.

- **GLAXOSMITHKLINE's Pandemrix vaccine** – Scientists may have found an explanation for the increased incidence of narcolepsy among people getting this H1N1 flu vaccine: a particular gene. Cases of narcolepsy associated with the vaccine have been reported in 12 countries, including 60 in Finland. Reportedly, all of the Finnish patients tested so far had the gene, which is known to increase the risk of developing narcolepsy.

- **Infusion pumps** – The FDA issued a Class I recall for **Medtronic**'s SynchroMed EL infusion system and its SynchroMed II programmable infusion pump, saying there is a potential problem with pocket fills occurring during refills that can result in both drug overdose and underdose. Faulty pumps have been linked to 8 deaths and 270 life-threatening injuries. However, Medtronic is not pulling the devices out of the field.

- **INHIBITEX's INX-08189**, a once-daily, oral guanosine nucleotide polymerase inhibitor, was granted fast track status by the FDA in hepatitis C. An ongoing Phase I trial is expected to finish this quarter.

- **MERCK's Movectro (cladribine)** – The company withdrew its European marketing authorization application for this oral multiple sclerosis drug after the European Medicines Agency decided there were not enough data for a positive recommendation.

- **NOVO NORDISK** was subpoenaed by the U.S. Attorney's Office for Massachusetts, which is investigating "potential criminal offenses relating to the company's marketing and promotion practices" for diabetes drugs Victoza (liraglutide), NovoLog (insulin aspart), and Levemir (insulin detemir).

- **NSF INTERNATIONAL**, an independent public health organization offering dietary supplement training, Good Manufacturing Practices (GMP) registration, testing and certification services, acquired **Pharmalytica Services**, a pharmaceutical contract laboratory.

- **PFENEX and BOEHRINGER INGELHEIM** entered into a strategic agreement giving Boehringer Ingelheim non-exclusive access to Pfenex's Expression Technology. Under the agreement, Pfenex will engineer production strains and processes for Boehringer's proprietary molecules as well as for molecules from Boehringer's contract manufacturing customers.

- **ROCHE/GENENTECH's Rituxan (rituximab)** – A randomized, multicenter, open-label, two-stage Phase III trial of a subcutaneous formulation of Rituxan + chemotherapy has been initiated in patients with CD20+ non-Hodgkin's lymphoma (NHL). The new formulation uses Enhanze technology from Halozyme Therapeutics.

- **SANOFI-AVENTIS** – It's final. Sanofi is buying **Genzyme**. And in making the announcement, a brand name for alemtuzumab for multiple sclerosis was revealed: Lemtrada.

- **STERIS** received a warning letter from the FDA saying the company is making unacceptable product claims for its sterilization system.

NEWS IN BRIEF

ACTELION's clazosentan – failed to show hemorrhage benefit

Clazosentan, an endothelin-receptor antagonist, missed the primary endpoint in the CONSCIOUS-2 trial, failing to show a significant benefit vs. placebo in the composite of all-cause mortality, vasospasm-related new cerebral infarcts, delayed ischemic neurological deficit due to vasospasm, and rescue therapy within six weeks of the hemorrhage.

CONSCIOUS-2 was a randomized, double-blind, international trial in 1,147 patients with aneurysmal subarachnoid hemorrhage treated with surgical clipping.

The results were presented at the American Stroke Association's International Stroke Conference. At six weeks:

- 21% of clazosentan patients and 25% of placebo patients met the primary endpoint ($p=0.1$).
- The drug failed to show a significant benefit vs. placebo in clinical functional outcome, a secondary endpoint (29% vs. 25%, $p=0.1$).
- Two subgroups of patients did show a benefit on the primary outcome: (a) those with WFNS grade ≥III had a 33% relative reduction, and (b) those with a diffuse thick subarachnoid hemorrhage had a 25% relative reduction.

- Side effects were more common with clazosentan, especially treatment-emergent lung complications (34% vs. 18%), anemia (22% vs. 15%), and hypotension (12% vs. 4%).

The results of another trial, CONSCIOUS-3, in aneurysm patients whose hemorrhages were treated with endovascular coiling instead of clipping, are not known, and the company has not made a decision as to whether development of the drug should continue.

Baldness – is a cure on the horizon?

Researchers at the Salk Institute reported in the journal ***PLoS One*** on their surprising finding that astressin-B grew hair on mice that were genetically engineered to be bald (hairless). The researchers were looking at the effects of blocking the stress hormone corticotrophin-releasing factor (CRF) on gastrointestinal function but found, instead, that the mice regrew all their lost hair. Further study convinced the researchers that astressin-B is more effective than minoxidil, which is approved to treat hair loss. However, human clinical trials are probably at least five years away.

Breast implants – are plastic surgeons downplaying the risks?

Sidney Wolfe, MD, and Michael Carome, MD, of Public Citizen's Health Research Group, wrote to FDA Commissioner Dr. Margaret Hamburg and Dr. Jeffrey Shuren, director of the FDA's Center for Devices and Radiological Health (CDRH), charging that two plastic surgery associations are encouraging doctors to mislead patients about the cancer risk with breast implants. In late January the FDA warned that it had found an apparent association between breast implants (both saline and silicone) and anaplastic large cell lymphoma (ALCL), a very rare type of cancer.

Public Citizen claimed that the presidents of the American Society of Plastic Surgeons and the American Society for Aesthetic Plastic Surgery hosted the members-only webinar during which they told their members to downplay the ALCL risk and characterize ALCL as a rare "condition," not cancer. The letter charged, "This campaign is misleading, dangerous, and unethical."

The American Society of Plastic Surgeons responded that it had no intent to downplay the issue, "Far from intending to trivialize or minimize the issue, [but] the type of ALCL that has been observed in possible association with breast implants does not appear to have the malignant course of classic ALCL, which is a systemic disease…Our position is and has always been that ALCL associated with breast implants is a serious, but an extremely rare condition."

Felmont Eaves, MD, president of the American Society for Aesthetic Plastic Surgery, told ***MedPage Today*** advising doctors to use the word "condition" instead of "cancer" wasn't the "best wording," adding, "No one is trying to say it's anything other than what it was defined as, which is ALCL."

BOEHRINGER INGELHEIM's Pradaxa (dabigatran) – new guidelines support AFib use

The American College of Cardiology, the American Heart Association, and the Heart Rhythm Society jointly issued new guidelines on the use of this blood thinner, recommending it as an alternative to warfarin to prevent blood clots and stroke in patients with either paroxysmal or permanent atrial fibrillation (AFib).

Hemodialysis – patients want more information

The results of a 1,000-patient survey conducted on the internet by the American Association of Kidney Patients and published in the ***Clinical Journal of the American Society of Nephrology*** indicated that dialysis patients are only "moderately satisfied" with their treatment and want more information on treatment options.

- 30% said that in-center hemodialysis, peritoneal dialysis, home hemodialysis, and kidney transplantation were not "equally or fairly" presented to them.
- Patient satisfaction was highest among transplant and home dialysis patients and lowest among those receiving in-center dialysis.
- Almost 70% said they were not provided specific education and training about home hemodialysis.

JOHNSON & JOHNSON

- **Procrit (epoetin alfa) –** The FDA rejected J&J's request to promote a less-frequent dosing schedule for this anemia drug, which currently is labeled for TIW administra-tion in patients with chronic kidney failure.
- **Invega Sustenna (paliperidone palmitate) –** The company recalled 70,000 pre-filled syringes of this anti-psychotic after finding cracks in some syringe barrels that could affect the drug's sterility, though no adverse reactions have been reported.

REGULATORY NEWS

CDC worried about opioid abuse

Mortality rates for heart disease and cancer are declining, but Thomas Frieden, MD, MPH, director of the Centers for Disease Control and Prevention (CDC), is worried that the "[only mortality statistic] getting worse is death from prescription opioid abuse." According to CDC data, 27,000 people died from prescription drug overdoses in 2007, a five-fold increase since 1990. U.S. drug czar Gil Kerlikowske said the prescription painkiller epidemic is at the top of the Obama administration's list of priorities in this field.

FDA device approval speed being scrutinized

Rep. Joe Pitts (R-PA), chairman of the House Energy and Commerce's Health Subcommittee, plans to look into why European regulatory agencies approve medical devices faster than the FDA: "I want us to explore why Europe has gained such a significant advantage over American companies."

FDA device overview questioned

A study by the National Research Center for Women & Families, published in the ***Archives of Internal Medicine***, found that 92 of 113 medical devices recalled by the FDA between 2005 and 2009 because of increased risk of serious harm or death had been approved for marketing under the 510(k) pathway without clinical studies or were exempt from FDA regulation. Furthermore, the FDA did not require post-marketing studies to determine safety and efficacy of these devices.

Diana Zuckerman, PhD, president of the National Research Center for Women & Families, said, "We found that some of these devices were approved by the FDA using these lower standards even though the FDA admits they were high-risk medical devices. The FDA is supposed to hold certain devices to this higher standard, and they are not doing it. They are classifying some products as moderate risk, even though some might kill you."

FDA drug approvals hindering innovation?

A report by the California Healthcare Institute and the Boston Consulting Group reported that the FDA spent an average of 18.9 months reviewing new drug applications (NDAs) submitted in 2008 vs. 14.8 months in the five-year period ending in 2007. The report also said that this 28% increase in review time hinders innovation and undermines U.S. competitiveness.

FDA eases pathway for hardware/software medical devices

The FDA announced a final rule down-classifying some medical software devices. Now, Medical Device Data Systems (MDDS) – off-the-shelf or custom hardware/software products used alone or in combination that display unaltered medical device data, or transfer, store, or convert medical device data for future use, in accordance with a preset specification (e.g., devices that collect and store data from a glucose meter for future use) – are Class I or low-risk devices.

Prior to this, the devices were either Class III or required a PMA. The FDA's Dr. Shuren said, "This rule is a common-sense regulatory approach that provides clarity and predictability for manufacturers of these data systems."

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

- **CELGENE's Vidaza (azacitidine)** – NICE reversed its position and endorsed coverage for this treatment for myelodysplastic syndrome. A NICE official said, "It is a very expensive drug, but the manufacturers have submitted a patient-access scheme where the cost will be reduced."
- **CELLERATION's MIST Therapy system** – NICE set a March 10, 2011, deadline for comments on this low-intensity ultrasound therapy for acute and chronic wounds. NICE's medtech advisory panel strongly encouraged further research on the device.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	February 2011	
February 25	Discuss and make recommendations on the selection of **strains to be included in the influenza virus vaccine** for the 2011-2012 influenza season and hear an update on Pandemic Influenza Surveillance	FDA's Vaccines and Related Biological Products Advisory Committee
	March 2011	
March 2	Discussion of **approaches to the development of drugs for orphan and rare disease**, including how to utilize biomarkers and pharmacogenetics	FDA Pharmaceutical Sciences and Clinical Pharmacology Advisory Committee meeting in Dallas, Texas
March 2	Session on how to prepare NDAs/ANDAs for **sodium fluoride F18** as a PET imaging agent	FDA public meeting
March 5 (approx.)	**Merck KGaA's cladribine** for multiple sclerosis	PDUFA date
March 7	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
March 8	**Novartis's Arcapta Neohaler** (indacaterol maleate), a QD bronchodilator for long-term use in COPD	FDA's Pulmonary-Allergy Drugs Advisory Committee
March 8-9	Recommendation on scientific issues concerning direct-to-consumer (DTC) genetic tests that make medical claims	FDA's Molecular and Clinical Genetics Advisory Committee
March 10	**Roche/Genentech's Lucentis** (ranibizumab) Phase III RISE results in DME	The Macula Society meeting
March 10	Risk of **neurodegeneration in pediatric patients** from anesthetic drugs	FDA's Anesthetic and Life Support Drugs Advisory Committee
March 10	**GlaxoSmithKline's Lamictal XR** (lamotrigine extended-release) and discussion of use of historical-controlled trials as a comparator for anticonvulsant monotherapy in epileptic seizures	FDA's Peripheral and Central Nervous System Drugs Advisory Committee
March 10	**Human Genome Sciences/GSK's Benlysta** (belimumab) for lupus	PDUFA date
March 15	Innovative Pathway for medical devices	FDA public hearing
March 16	Preliminary decision on **how to cover ESAs** for kidney disease patients	CMS decision
March 26	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for advanced melanoma	PDUFA date
	April 2011	
April 2	**Novartis's Gleevec** (imatinib) for GIST	PDUFA date
April 5	**Optimer Pharmaceuticals' fidaxomicin** for the treatment of *C. diff*	FDA Anti-Infective Drugs Advisory Committee
April 7	**AstraZeneca's Zactima** (vandetanib) for inoperable medullary thyroid cancer	PDUFA date
April 7-8	**FDA 510(k) reform**	FDA public meeting
April 10	Open forum to discuss statistical issues related to **drug and biologics development and review**	Joint FDA and Drug Information Agency Forum
April 13	**KV Pharmaceutical/Hologic's Gestiva** (17-alpha hydroxyprogesterone) to prevent premature birth	PDUFA date
	Other future 2011 meetings/events	
May 23	**Vertex Pharmaceuticals' telaprevir**, a treatment for hepatitis C	PDUFA date
May 30	**Optimer Pharmaceuticals' fidaxomicin** for the treatment of *C. diff*	PDUFA date
June 16	Final decision on **coverage of ESAs** for kidney disease patients	CMS decision
June 23	**Pfizer/King Pharmaceuticals/Pain Therapeutics' Remoxy** (tamper-resistant oxycodone CR) for pain	PDUFA date
July 20	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	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 from 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 20	**Johnson & Johnson's abiraterone** for metastatic prostate cancer	PDUFA date
December	**Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to complete	Company announcement or medical conference presentation
	2012 meetings/events	
February 2012	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation