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…

SHORT TAKES

- **Addiction –** The American Society of Addiction Medicine is redefining addiction as a chronic brain disorder and a primary disease that should be treated as any other chronic disease, not treated as a moral or criminal or social problem.
- **AEGIS THERAPEUTICS' ProTek –** The company was issued a patent for certain methods using this technology designed to increase the stability of GLP-1 peptide analogs (diabetes drugs) and to allow them to be delivered by injection, nasal spray, or pill.
- **Antiviral therapy –** Massachusetts Institute of Technology's Lincoln Lab researchers developed a technique that so far has killed 15 viruses – including H1N1 influenza, poliovirus, dengue hemorrhagic fever, and bunyavirus – by chemically targeting viral-infected cells to get them to self-destruct. The researchers now plan to test double-stranded RNA [dsRNA] Activated Caspase Oligomerizer (DRACO) on HIV.
- **Antipsychotics –** Sen. Charles Grassley (R-IA) and Sen. Herb Kohl (D-WI) called again for the Centers for Medicare and Medicaid Services (CMS) to closely monitor prescriptions for atypical antipsychotics in nursing homes and to look into whether pharmacy benefit managers are responsible in any way for expanding the use of these drugs in Medicare patients.
- **APRICUS BIOSCIENCES/NEXMED USA's tolnaftate-D**, an antifungal therapy that uses its NexACT transdermal drug-delivery system, was approved by the FDA for over-the-counter (OTC) sale.
- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran) –** Japan's Ministry of Health, Labor, and Welfare issued a safety advisory against this oral direct thrombin inhibitor for the prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation (AFib) after five patients died. There have been 81 cases of serious side effects, including gastrointestinal bleeding, since the drug's launch in Japan in January 2011.
- **DARA BIOSCIENCES' KRN-5500**, a treatment for chemotherapy-related neuropathic pain, was granted fast track status by the FDA. The company plans to collaborate with the National Cancer Institute (NCI) on a second Phase II trial, which is expected to start later this year.
- **HPV vaccine –** Blue Cross Blue Shield of Massachusetts said it will start covering papillomavirus vaccine for adult men and boys.

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- **MEDTRONIC's CoreValve**, a transcatheter aortic valve, received a CE Mark.
- **Prosthetics** – Delaware has a new law that requires health insurers operating in the state to cover amputees needing prosthetic care and devices at a rate similar to other medical services. Nineteen other states have similar prosthetic parity laws.
- **PROTALIX BIOTHERAPEUTICS' taliglucerase alfa** – The FDA accepted a new drug application (NDA) for this Gaucher's disease drug. In February 2011, the FDA asked Protalix for more clinical trial data before any filing.
- **Radiation therapy** – Merging a standard MRI machine with a linear accelerator to create a new radiation device may change cancer treatment by giving doctors real-time images during treatment, which can help them precisely pinpoint tumors. The technology was invented at Canada's Cross Cancer Institute, which said clinical trials will begin in about three years.
- **REGENERON PHARMACEUTICALS' Eylea (aflibercept, VEGF Trap-Eye)** – The FDA extended the review period for this wet AMD drug by three months – to November 18, 2011.
- **ROCHE's Zelboraf (vemurafenib)** and the companion cobas 4800 BRAF V600 Mutation Test, a treatment for BRAF V600E mutation-positive metastatic melanoma with an accompanying diagnostic test to identify eligible patients, was approved by the FDA.
- **SEATTLE GENETICS/TAKEDA's Adcetris (brentuximab vedotin)** was approved by the FDA to treat Hodgkin's lymphoma and systemic anaplastic large cell lymphoma (ALCL).
- **Transcatheter aortic valve implantation (TAVI)** – A study in the ***Journal of the American College of Cardiology: Cardiovascular Interventions*** found the risk of vascular complications with TAVI increases with the sheath-to-femoral-artery ratio (SFAR). An SFAR of 1.05 predicted a four-fold increased risk of major complications and 30-day mortality, and more than 25% of those patients had vascular complications.

NEWS IN BRIEF

ASPECT MEDICAL's BIS – study found it less effective than expected

A study published in the ***New England Journal of Medicine*** found that this device which measures the bispectral index of electrical brain activity to monitor for rare cases of unintended intraoperative awareness was no better than using a measure of the concentration of anesthetic gases (ETAC) in a patient's breath. In fact, there were fewer cases of intraoperative awareness among patients in whom gas concentrations were measured vs. those whose brain activity was monitored.

CYTOKINETICS' omecamtiv mecarbil – promising results in heart failure

This myosin activator, improved cardiac function in two heart failure studies published in ***The Lancet***.

- In a U.S. study of 34 healthy volunteers, the researchers found the maximum tolerated dose is a 6-hour infusion of 0.5 mg/kg per hour. This study also found a dose-dependent increase in cardiac function with omecamtiv.
- In a 45-patient, double-blind, dose-escalation, crossover, Phase II study, U.K. researchers reported that the drug dose-dependently increased systolic ejection time, stroke volume, and fractional shortening vs. placebo.

Two of three patients who had plasma concentration greater than 1,200 ng/mL did not tolerate it well.

These studies suggest that omecamtiv is generally well tolerated in patients with stable heart failure over a broad range of plasma concentrations. However, the researchers cautioned that improvement in cardiac function has not been shown to result in improved outcomes. Currently, this is an IV drug, but the company is working on an oral formulation.

Drug-eluting stents – limiting use could save $

A study in ***Circulation*** found that limiting the use of drug-eluting stents (DES) does ***not*** increase the risk of heart attack or death but could save the U.S. healthcare system hundreds of millions of dollars a year. The analysis of 10,144 angioplasty patients found the use of DES dropped from 92% in 2004-2006 to 68% in 2007, but the rates of heart attack and death stayed about the same. The selective use of DES reduced medical costs by ~$400 per person.

GILEAD SCIENCES' Quad – positive results in HIV

The company said a single "quad" pill, an antiretroviral combination of **Truvada (emtricitabine + tenofovir) + elvitegravir + cobicistat** for the treatment of HIV, was found to be non-inferior to Gilead's three-drug formulation **Atripla (efavirenz + emtricitabine + tenofovir)** in a Phase III trial. That trial showed 88% of new patients taking the quad pill had undetectable levels of HIV in their blood after 48 weeks of therapy vs. 84% of patients taking Atripla. Gilead said the average 48-week increase in CD4-positive T cells was significantly greater for patients taking the quad pill vs. Atripla and that the study will continue for another 48 weeks to test longer-term safety and tolerability.

IMPAX PHARMACEUTICALS and GLAXOSMITHKLINE's IPX-066 – more positive results in Parkinson's disease

A second Phase III trial, ASCEND-PD, of this extended release formulation of carbidopa-levodopa found advanced Parkinson's disease patients taking the drug had an 84-minute improvement in "off time" and a corresponding increase in "on time" without dyskinesia vs. patients taking the formulation plus entacapone. The companies plan to submit the drug to the FDA in 4Q11.

JOHNSON & JOHNSON/MCNEIL's Tylenol (acetaminophen) – yet another recall

J&J said it is recalling certain lots of its Tylenol Cold Multi-Symptom Nighttime Rapid Release Gelcaps manufactured before its Fort Washington PA plant closed in April 2010.

PFIZER

- **Crizotinib.** European regulators are reviewing this drug for advanced non-small cell lung cancer (NSCLC).
- **Bosutinib.** European regulators are reviewing this drug for chronic myeloid leukemia (CML).

Pharma advertising – most ads not FDA compliant

A study reported in ***PLoS ONE*** found most pharma ads in biomedical journals do not conform with FDA advertising guidelines. The researchers reviewed 192 ads for 82 products in 12 journals and found:

- Only ~18% complied fully with all the FDA rules.
- 58% did not calculate serious adverse events, including death.
- 48% did not have references that could be confirmed.
- 29% did not quantify effectiveness adequately.

SIRTRIS PHARMACEUTICALS' SRT-1720 – potential obesity drug

In a study published in ***Scientific Reports***, researchers from the National Institute on Aging reported that obese mice lived up to 44% longer when given a high dose of this Sirt1 activator despite continuing to eat a high-fat diet. They also had less fat accumulation in their liver, improved pancreas morphology, and more normal oxygen consumption and locomotor activity. However, obese mice who had their diet changed to a standard (not high-fat) diet but didn't get SRT-1720 lived the longest. No toxicity was reported out to 80 weeks. The applicability of the findings to humans is not yet known.

TAPIMMUNE's breast and ovarian cancer vaccine – trials to begin

The FDA said trials can begin at the Mayo Clinic for a vaccine to protect against breast and ovarian cancer. TapImmune's vaccine, which is designed to be given after breast cancer patients receive conventional chemotherapy, targets the HER2/neu molecule, which helps tumors grow. The vaccine contains fragments of the folate receptor alpha protein and teaches the body's immune system to detect and eliminate diseased cells and prevent relapse. The vaccine is scheduled to start human clinical trials in 4Q11 in combination with GM-CSF to enhance immunity.

TNF inhibitors – increase skin cancer risk

A study in ***Rheumatology*** found rheumatoid arthritis (RA) patients treated with tumor necrosis factor (TNF) inhibitors had about a third higher risk for non-melanoma skin cancer vs. similar patients treated with non-biologic disease-modifying antirheumatic drugs (DMARDs). Data from >20,000 U.S. military veterans showed the incidence of non-melanoma skin cancer was 18.9 per 100 patient-years in patients given TNF inhibitors vs. 12.7 per 100 patient-years in patients on non-biologic DMARDs. An increased risk was seen in patients who were older, male, had used nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids, or had prior malignancies.

U.S. drug supply – worsening shortages and rising gray market prices

The FDA said more than a dozen cancer drugs are now in short supply in the U.S., and the situation is getting worse due to various reasons, particularly manufacturing quality problems.

The Agency said there were 178 drug shortages in 2010, three quarters of which were sterile injectables, including chemotherapy infusions. So far in 2011, there have been 180 drug shortages. A study of 311 hospitals by Premier found 96% of drugs offered by 18 gray marketers were double the legitimate price, 45% were 10 times the normal price, and 27% were at least 20 times the normal price.

Wireless medical devices – safety concerns

Rep. Anna Eshoo (D-CA) and Rep. Ed Markey (D-MA) want the Government Accountability Office (GAO) to investigate whether the Federal Communications Commission (FCC) is doing everything possible to make sure wireless medical devices are safe. The legislators sent a letter to the GAO citing a recent demonstration at a hacker conference where it was shown how to remotely control these devices, including pacemakers, intravenous pumps, and blood pressure cuffs.

REGULATORY NEWS

FDA: Drug names

The Pharmaceutical Research and Manufacturers of America (PhRMA) told the FDA that drug name reviews need to be overhauled or repealed, saying there are no validated ways to determine when two proprietary names are similar.

FDA issues device postmarket surveillance guidelines

The FDA issued guidance on what types of devices can be eligible for – and how manufacturers should comply with – postmarket surveillance programs. The guidance says that a postmarket surveillance study can be required at any point during a device's lifecycle. It also recommends the 36-month surveillance period be extended for pediatric devices.

FDA issues PMA guidance

The FDA issued draft guidance to help manufacturers design better-quality premarket approval (PMA) applications for medical devices, including:

- Minimizing data bias and variability.
- Setting appropriate study objectives.
- Selecting the appropriate type of study.
- Choosing study sites and study participants.

The guidance also included ways to assess benefit vs. risk during the PMA process, including a draft worksheet FDA reviewers may use that includes factors such as levels of uncertainty in the probability of a harmful event and patient tolerance for risks in light of their medical condition. The guidance includes some interesting hypothetical examples at **www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm#5**

FDA issues final rule for three Class III devices

The FDA issued a final rule requiring makers of ventricular bypass devices, female condoms, and pacemaker repair/replacement materials to use the premarket approval (PMA) pathway for their devices instead of the 510(k) pathway.

FDA: User fees

The FDA and generic drugmakers reached an agreement on user fees to speed up the approval process and increase the rate of inspections of factories in other countries. The program, which is subject to congressional approval, calls for the Agency to collect $299 million in the first year in annual fees for underwriting of biennial inspections of foreign plants.

FDA approvals/clearances

- **AVINGER's Wildcat** – a catheter for patients with peripheral artery disease (PAD) that creates a small channel in totally blocked peripheral arteries, enabling subsequent treatment via balloon angioplasty, stent, or atherectomy.
- **INTERSECT ENT's Propel (mometasone furoate)** – a drug-releasing implant for patients with chronic sinusitis.
- **INTRICON's Centauri Ambulatory Patient ECG** – a wireless tracking device that can alert healthcare providers of a patient's risk of heart arrhythmia.
- **ORTHOCOR MEDICAL's Alleva** – an OTC line of heat and cold wraps designed to alleviate pain (either general or arthritic).
- **TOSHIBA/VITAL IMAGES' VitreaView** – a system that allows clinicians to view patient images in a uniform manner through health information exchanges and electronic health records (EHRs).

FDA recalls

- **PFIZER**
  - **Advil Congestion Relief tablets** – because of a failure to meet dissolution specifications.
  - **Citalopram** – 10 mg 100-count bottles made in India because of a label mix-up.

- **Procardia XL (nifedipine)** – due to a failed dissolution test.

- **TEVA PHARMACEUTICALS' glipizide tablets** – because of impurities/degradation products and out-of-specification impurity result.
- **TOSHIBA AMERICAN MEDICAL SYSTEM's Aplio Artida Ultrasound Diagnostic System SSH-880CV** – because the panel operation for this ultrasound device may fail to properly display patient information, such as heart rate, time, VCP counter, etc.
- **UPSHER-SMITH LABORATORIES' Jantoven (warfarin)** – due to a report of a bottle of labeled 3 mg tablets actually containing 10 mg tablets. The recall was expanded to several other tablets: oxybutynin chloride, baclofen, Androxy (fluoxymesterone), amantadine hydrochloride, and amlodipine besylate.

European approvals

NEUROLOGICA's inSPira HD, a portable, high-resolution SPECT camera, received a CE Mark.

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

NOVARTIS' Tasigna (nilotinib) for chronic myeloid leukemia (CML) got a thumbs-up after the company agreed to give the National Health Service (NHS) a discount.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	August and September 2011	
August 25	**Shire's Firazyr** (icatibant injection) for hereditary angioedema	PDUFA date
September 2011	**Drug shortages**	FDA public meeting
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 and Drug Safety and Risk Management Advisory committees
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
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 30	Institute of Medicine's recommendations for FDA's reform of the **510(k) device clearance program**	Public comment deadline
	October 2011	
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 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
	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 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), 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