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

- **Advanced Hodgkin's lymphoma –** A seven-drug regimen improves initial tumor control better than the standard regimen, according to a study in the ***New England Journal of Medicine***.
- **AMERICAN REGENT's calcium gluconate injection –** The company is recalling this product because it may contain silicone particles.
- **AVID RADIOPHARMACEUTICALS and LILLY's Amyvid (florbetapir) –** Avid said it is working with the FDA to develop a training program for this PET agent for diagnosing Alzheimer's disease. An FDA advisory panel in January 2011 said the drug may delay or prevent the disease from progressing, but more data are needed to show the scans can be properly interpreted, and in March 2011 the FDA took that advice, rejecting the agent.
- **Blood testing kits –** The World Health Organization warned that blood testing kits used to detect active tuberculosis are unreliable and should be banned.
- **CEPHALON's Fentora (fentanyl buccal) and Actiq (oral transmucosal fentanyl citrate) –** The FDA approved the company's risk evaluation and mitigation strategy (REMS) for these cancer-related breakthrough pain drugs. Under the REMS, doctors who prescribe the drugs – and the dispensing pharmacies – have to enroll by completing an education "module" that focuses on safety and appropriate patient selection. Prescribers then will be expected to educate patients.
- **CHUGAI PHARMACEUTICAL's Actemra (tocilizumab) –** The company said a subcutaneous formulation of this rheumatoid arthritis therapy demonstrated non-inferiority in efficacy vs. intravenous infusion in a Phase III trial.
- **Contraceptives –** The National Academy of Sciences' Institute of Medicine is recommending that, under the new healthcare law, all insurers be required to cover contraceptives for women free of charge. Obama administration officials said the new requirements could take effect for many plans at the beginning of 2013.
- **Dementia and painkillers –** A 352-patient study published in the ***British Medical Journal*** found painkillers significantly reduced agitation in moderate-to-severe dementia patients. After eight weeks, there was a 17% reduction in agitation symptoms among patients taking painkillers vs. patients on their usual treatments, a greater improvement than would have been expected from treatment with antipsychotics.
- **EDWARDS LIFESCIENCES' Sapien –** The FDA's Circulatory System Devices Advisory Committee voted 9 to 0 with one abstention to recommend approval of this transcatheter aortic heart valve for symptomatic, inoperable patients with a native valve.

But the panel also wanted a slow, measured roll-out, with good training, and a comprehensive national registry.

- **ENDOLOGIX's Powerlink** – The company said it is ending its agreement with **LeMaitre Vascular**, which had been distributing its aortic endovascular system and related products in Europe.

- **EXPRESS SCRIPTS** plans to buy **Medco Health Solutions**. The merger would account for about four of every 10 prescription claims in the U.S. *The question is whether this can pass the Federal Trade Commission.*

- **Home medical devices** – The FDA and other government agencies and professional groups should work together to ensure home health devices are safe and easy to use, according to a National Research Council report that recommends the FDA promote the development of new standards for labels and guidelines on home medical devices.

- **IDERA PHARMACEUTICALS' IMO-3100** – The FDA told the company to postpone a Phase II trial of this treatment for psoriasis. The company said the FDA made the request verbally and has not yet given a reason.

- **LILLY's semagacestat** – Data presented at the Alzheimer's Association International Conference (AAIC) found patients with Alzheimer's disease whose condition worsened after taking this experimental drug did not improve even seven months after they stopped taking the drug.

- **LUPIN**, the fifth-largest supplier of generic drugs and the largest supplier of tuberculosis drugs, said it is considering selling its unit that markets drugs in India.

- **MERCK and ROCHE** plan to jointly promote their HCV drugs: Merck's Victrelis (boceprevir) and Roche's Pegasys (peginterferon alfa-2a).

- **NABI BIOPHARMACEUTICALS' NicVAX (nicotine conjugate)** – This experimental anti-smoking vaccine failed in a Phase III trial.

- **NOVARTIS' Ritalin (methylphenidate) and LILLY's Prozac (fluoxetine)** – A rat study published in the ***Journal of Neuroscience*** found that taking an attention-deficit/hyperactivity disorder (ADHD) drug along with an antidepressant appeared to "set in motion subtle changes in brain function that, in adulthood, makes an individual more sensitive to reward as well as to stress, and more likely to exhibit the pessimism and hopelessness seen in depression. Combination of the [drugs] appears to act on the brain in much the same way as does cocaine."

- **QRXPHARMA LIMITED's MoxDuo IR (morphine + oxycodone immediate-release)** – The company began the New Drug Application (NDA) approval process for this painkiller for the treatment of moderate-to-severe acute pain.

- **ROCHE/GENENTECH's GDC-0941** – A study of 97 patients presented at the American Society of Clinical Oncology (ASCO) found that this drug, which targets the P13K gene (which is abnormal in 20%-30% of patients with advanced breast cancer), may work in those patients.

- **SANOFI's Multaq (dronedarone)** – The FDA and the European Medicines Agency (EMA) issued safety alerts about this anticoagulant for abnormal heart rhythms, pointing to a study showing twice as many deaths in atrial fibrillation patients taking it vs. those not taking it.

- **SUN PHARMACEUTICAL INDUSTRIES EUROPE's doxorubicin SUN** – The company is withdrawing its European application for this hybrid generic 2 mg/ml concentrate solution for infusion, which was originally intended to be used to treat breast and ovarian cancer.

- **TAKEDA's Actos (pioglitazone)** – The EMA said this Type 2 diabetes drug may be kept on the market with new warnings about a small increased risk for bladder cancer, pointing to the FDA's decision that Actos was not linked to an overall increased cancer risk in all patients taking it.

- **TALON THERAPEUTICS' Marqibo (vincristine)** – The company filed for accelerated FDA approval for this capsule to treat Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL) in adults.

- **TRANSCEPT** plans to cut ~45% of its workforce after the FDA refused to approve its insomnia medicine Intermezzo (zolpidem tartrate sublingual).

- **VIRxSYS' VRX1273 vaccine** – The company said 40% of monkeys vaccinated with this genetically altered version of simian immunodeficiency virus (SIV), the version of HIV found in non-human primates, had very low-to-undetectable amounts of the virus in their bodies after 18 months.

NEWS IN BRIEF

ALLERGAN

- **Botox (onabotulinumtoxinA).** The company expects to cut its animal testing by 95% within three years since the FDA approved a new method to test the drug's potency. An FDA official said new testing methods like this one could make animal toxicity tests obsolete within 10-20 years.

- **Vicept Therapeutics.** Allergan is buying this dermatology company, which makes V-101, a topical cream for the treatment of erythema associated with rosacea.

Alzheimer's Association International Conference (AAIC, formerly the International Conference on Alzheimer's Disease) meeting in Paris

- **Predictability research.** Measuring tau and beta-amyloid proteins in cerebrospinal fluid in addition to MRI-based brain atrophy evaluation improves the ability to predict which patients with mild cognitive impairment (MCI) will progress quickly to Alzheimer's disease.
- **Retinal scans.** A pilot study using retinal scans to measure blood vessel thickness at the back of the eye showed strong correlations with the level of beta-amyloid deposits in the brain, according to an Australian researcher.

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 (ticagrelor).** This oral antiplatelet agent was approved by the FDA for preventing blood clots in patients with acute coronary syndrome.
- **Seroquel (quetiapine).** This antipsychotic drug's label is getting a new cardiac warning: Seroquel and Seroquel XR should be avoided in combination with at least a dozen other medicines linked to QT prolongation.

Boehringer Ingelheim's Pradaxa (dabigatran)

- **Serious adverse events.** The first analysis of 210 spontaneous reports of Pradaxa in France as part of the drug's risk management plan, which were to be reported at International Society of Thrombosis and Haemostasis (ISTH), found 44% of the cases were considered to be serious. There were six deaths: one from cerebral hemorrhage, one from gut ischemia, and four sudden deaths.

Pradaxa Adverse Events in France	
Most common adverse events	**n=210**
Bleeding	24%
PE/DVT	22%
Liver injury	11%

- **Increased MI risk.** Data to be presented at ISTH found more evidence of an increased myocardial infarction (MI) risk with this direct thrombin inhibitor in the Phase III RE-MEDY trial, showing a statistically significant increase in acute coronary syndromes in patients taking Pradaxa vs. warfarin (0.9% vs. 0.2%).

Bracco Diagnostics' CardioGen-82 – FDA warning

The FDA issued a warning about the potential for inadvertent, increased radiation exposure in patients who underwent or will be undergoing cardiac PET scans with rubidium-82 (Rb-82) chloride injection from this device. The Agency received reports of two patients who received more radiation than expected, due to strontium isotopes which may have been inadvertently injected into the patients from a problem with the device. The FDA said the risk of harm from the exposure is minimal, and the excess the two patients received is similar to other types of heart scans.

Elan's bapinezumab – more brain edema

A review of three Phase II trials of this drug presented at the AAIC meeting found cerebral vascular edema in patients treated with this monoclonal antibody specific for beta-amyloid protein plaques occurred much more frequently than previously reported. A central review of brain images of 262 patients showed 15 previously undetected cases of cerebral vascular edema in addition to the 21 cases identified earlier by study investigators. However, another study presented at AAIC found the risk of amyloid-related imaging abnormalities of edema/effusion, or ARIA-E, seems to decline over time in patients who stay on the drug.

GlaxoSmithKline

- **Pandemrix.** The EMA warned that this H1N1 vaccine should only be given to children and teenagers at risk of the flu if other vaccines are unavailable since 10 suspected cases of narcolepsy have been linked to the vaccine. The EMA said studies showed a 6- to 13-fold increased risk of narcolepsy in children and adolescents vaccinated with Pandemrix vs. unvaccinated children.

International AIDS Society Conference in Rome

- **Gilead Sciences' elvitegravir.** A study found this once-daily integrase inhibitor was non-inferior to twice-daily Merck's Isentress (raltegravir).
- **GlaxoSmithKline's Zovirax (acyclovir).** This herpes drug also curtails the progression of HIV, according to a study presented at the meeting. The reduction in the risk of progression was almost entirely driven by people who started the trial with a plasma viral load of >50,000 copies of HIV RNA per ml.

- **GlaxoSmithKline and Pfizer's dolutegravir.** A study found this HIV drug controlled HIV faster and more safely than **Bristol-Myers Squibb's Sustiva (efavirenz)**. Investigators said dolutegravir reduced HIV to undetectable levels in 90% of patients after 48 weeks vs. 82% of Sustiva patients.
- **Lilly and Kowa Pharmaceuticals America's Livalo (pitavastatin).** A study found this cholesterol-lowering drug appears to work well with HIV drugs.
- **ViiV Healthcare's lersivirine (UK-453061).** The 48-week results of an ongoing 96-week Phase IIb trial found that 79% of patients on either dose (500 mg or 750 mg) of this once-daily non-nucleoside reverse transcriptase inhibitor was as effective as 600 mg Sustiva in treatment-naïve patients, with 79% of lersivirine patients achieving undetectable HIV RNA vs. 86% with Sustiva. The issue with lersivirine is nausea, which occurred in 23% of patients on 500 mg and in 42% of patients on the 750 mg dose vs. 13% of Sustiva patients. However, three other side effects were much less frequent with lersivirine: dizziness (6%-8% vs. 21%), abnormal dreams (8% vs. 19%), and rash (2%-3% vs. 11%).

JOHNSON & JOHNSON – no recalls this week

Not only were there no new recalls this week, but J&J offered an explanation for past recalls. The company said its massive number of product recalls in 2010 were the result of poor management, staffing cuts, and "breakdowns in integrating the consumer unit it bought from Pfizer."

Massachusetts Blue Cross/Blue Shield – unresponsive mental health requests

A study on mental health coverage in Massachusetts showed poor response to Harvard researchers posing as patients insured by BCBS and needing an appointment for depression. The researchers called every mental health facility within a 10-mile radius of downtown Boston, saying they had been diagnosed with depression and needed to see a psychiatrist within two weeks. Only eight of the 64 facilities listed as preferred providers made an appointment, and only four said an appointment could be made within two weeks.

Multiple sclerosis (MS) – drugs are *not* cost-effective

A study published in ***Neurology*** found the benefit of MS drugs comes at a high cost vs. basic therapy to control symptoms. The principal investigator said, "MS drugs are not cost-effective …under the current prescribing and pricing conditions in the U.S., with drugs accounting for more than 50% of a person's overall healthcare related costs over 10 years."

The study reviewed data from 844 relapsing MS patients and found disease-modifying drugs resulted in modest health gains, but the cost-effectiveness was >$800,000 per quality-adjusted life year (QALY). For example, patients taking interferon beta-1a (**Biogen's Avonex**) gained ~2 quality-adjusted ***months*** over 10 years vs. those who did not take the drugs, and they were relapse-free for 6 out of 10 years vs. 5 out of 10 years for non-users.

NOVARTIS

- **Ilaris (canakinumab).** Public Citizen's Health Research Group wants the FDA to suspend studies of this human monoclonal antibody targeted at interleukin-1 beta, saying the studies are unethical and do not protect humans, including children. The drug is approved for the treatment of cryopyrin-associated periodic syndrome (CAPS) and is under investigation to treat diabetes.

  Public Citizen is asking the FDA to assess all ongoing clinical trials involving Ilaris and to stop two trials – one in which 7,200 adult heart attack patients are given Ilaris or placebo to see if the drug decreases the risk of further heart attacks, strokes, and death from cardiovascular disease; and a National Institutes of Health (NIH) funded study of 66 patients ranging in age from six to 45 years old with newly diagnosed Type 1 diabetes given Ilaris or placebo for one year to see if their pancreases still produced insulin.

  Novartis is conducting studies of Ilaris in patients with Type 2 diabetes, osteoarthritis, and polymyalgia rheumatica, etc., but Public Citizen said just one dose of the drug has many serious risks.
- **Meningococcus B vaccine.** Novartis, along with researchers at the University of Florence, Italy, working to engineer 54 immunogens, found the protein that induces the strongest antibody response in a mouse model, according to a study published in ***Science Translational Medicine***. The researchers wrote, "We demonstrate that the structure-based design of multiple immunodominant antigenic surfaces on a single protein scaffold is possible and represents an effective way to create broadly protective vaccines."

Osteoporosis drugs – linked to esophageal cancer

The FDA warned doctors and patients about a potential increased risk of esophageal cancer with oral osteoporosis drugs, including:

- **Merck's Fosamax (alendronate)**
- **Warner Chilcott's Actonel (risedronate)** and **Atelvia (risedronate delayed-release)**
- **Roche's Boniva (ibandronate)**

- **Norwich's Didronel (etidronate)**
- **Sanofi's Skelid (tiludronate)**

PFIZER

- **Buying Icagen**, a small biopharmaceutical company that is developing pain drugs.
- **Chantix/Champix (varenicline).** In the U.S., Chantix is getting a new, updated label that includes information on both efficacy and safety in patients with cardiovascular disease or chronic obstructive pulmonary disease (COPD) as well as alternative directions for patients to select a quit smoking date. In addition, an EMA committee said the increased risk of cardiovascular events found in a meta-analysis of possible side effects with Champix (the European brand name) does ***not*** outweigh the benefits of this anti-smoking drug.
- **Torcetrapib.** This HDL-raising drug may have helped control Type 2 diabetes in the failed ILLUMINATE trial, according to an Australian post hoc study published in the ***Journal of the American Heart Association***. Torcetrapib appeared to modestly but significantly reduce serum glucose, HbA_{1c}, and insulin levels and cut insulin resistance when added to Pfizer's **Lipitor (atorvastatin).**

ROCHE

- **Buying mtm laboratories**, a German *in vitro* diag-nostics company that focuses on early detection and diagnosis of cervical cancer. Mtm will become part of Roche's Tissue Diagnostics (Ventana Medical Systems) business unit.
- **Omnitarg (pertuzumab).** Roche said it will submit this monoclonal antibody to treat breast cancer to the FDA by the end of 2011.

Statins – no increased cancer risk

A study published in the ***Journal of the American College of Cardiology*** found no increased cancer risk in statin users. The investigators said, "After an average five years of follow-up among nearly 46,000 pairs of people who either used the cholesterol-lowering drugs or did not use them, 11.37% of participants taking a statin developed cancer compared to 11.11% of those individuals not taking a statin."

WATSON PHARMACEUTICALS' Trelstar (triptorelin) – may preserve fertility in breast cancer patients

Premenopausal breast cancer patients treated with this gonado-tropin-releasing hormone (GnRH) analog had significantly less chemotherapy-induced early menopause vs. those not treated, according to the Promise-GIM6 study published in the ***Journal of the American Medical Association*** (JAMA). Forty percent of women under 40 undergoing chemotherapy for breast cancer become infertile, but triptorelin reduced that by >17%.

REGULATORY NEWS

FDA down-classifying ECG electrodes

The FDA is classifying e**lectrocardiograph (ECG) electrodes** as Class II devices and excepting them from the premarket (PMA) notification requirement.

FDA defends 510(k) review times

An analysis by the FDA's Center for Devices and Radiological Health (CDRH) of the FDA's 510(k) program found that premarket review times are steadily increasing due primarily to an increase in the number of review cycles and the amount of time companies take to respond to requests for additional information. The analysis blamed poor submission quality and sponsor failure to address deficiencies that were initially identified for the increase in total review times.

FDA innovation initiative

FDA Commissioner Margaret Hamburg, MD, said the Agency is launching an "innovation initiative" to make product development and regulatory approval easier for U.S. businesses. The FDA will establish an "entrepreneur in residence" to help small companies navigate the regulatory review process.

FDA oversight of mobile medical apps

The FDA has proposed oversight of certain mobile applications specific to medicine (medical apps) designed for iPhones and other mobile computing devices, and the Agency is now seeking public comment on the proposal. The draft guidance defines a small subset of mobile medical apps that impact or may impact the performance or functionality of currently regulated medical devices, including those:

- Used as an accessory to FDA regulated devices – e.g., an app that allows a doctor to make a specific diagnosis by viewing an image from a picture archiving and communication system (PACS) on a smartphone or iPad.
- That transform a mobile communications device into a regulated device by using attachments, sensors, or other devices – e.g., an app that turns a smartphone into an ECG machine.

European approvals

- **AMGEN's Xgeva (denosumab)** – for preventing fractures and other skeletal events in adults with solid tumors.
- **JOHNSON & JOHNSON:**
  - **Incivo (telaprevir)** – for hepatitis C.
  - **Zytiga (abiraterone acetate)** – for prostate cancer.
- **MERCK's Victrelis (boceprevir)** – for hepatitis C.

FDA adverse events watch list

The FDA published its 1Q11 list of drugs it is monitoring for safety risk. Notably, **Sanofi's Multaq (dronedarone)** is on the list for the fifth straight time due to potential signs of renal impairment and failure. The other drugs on the list were:

- **Abbott's Humira (adalimumab)**
- **Boehringer Ingelheim's Pradaxa (dabigatran)**
- **CSL Behring's Vivaglobin (human immune globulin)**, which was taken off the market in April 2011
- **GlaxoSmithKline's Requip (ropinirole HCl)**
- **Lilly and Bristol-Myers Squibb's Erbitux (cetuximab)**
- **Lilly's Effient (prasugrel HCl)**
- **Luitpold Pharmaceuticals' Venofer (iron sucrose injection)**
- **Omrix Pharmaceuticals' Evicel and Baxter Healthcare's Tisseel VH (fibrin sealant)**
- **Prometheus' Imuran (azathioprine)**
- **Roche's Rituxan (rituximab)**
- **Taro Pharmaceutical's Ovide (malathion)**
- **Teva's Purinethol (mercaptopurine)**

FDA approvals/clearances

- **EDWARDS LIFESCIENCES' EV1000** – 510(k) clearance for this monitoring tool designed to facilitate decision making in intensive care units and operating rooms.
- **Flu vaccine** – The FDA approved the vaccine for the 2011-2012 season; it will be used by the six manufacturers licensed to produce and distribute it. The strains selected:
  - A/California/7/2009 (H1N1)-like virus (pandemic H1N1) 2009 influenza virus
  - A/Perth/16/2009 (H3N2)-like virus
  - B/Brisbane/60/2008-like virus
- **SIEMENS HEALTHCARE's syngo Neuro PBV IR** – A software tool in the diagnosis and treatment of aneurysms and other vessel malformations as well as strokes.

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

EISAI's Halaven (eribulin mesylate) – NICE rejected this breast cancer drug, saying it is too expensive and the benefits do not outweigh the risks.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	July 2011	
July 25	Discussion about **drugs and safety**	Public Citizen and FDA Commissioner Margaret Hamburg, MD
	August 2011	
August 12	**Physician-owned distributorships (PODs)**	Inspector General initial report due to Senate Finance Committee
August 19	FDA's draft **Strategic Plan for Regulatory Science**, including an update on the Nanotechnology Program	FDA's 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
	Other 2011 meetings/events	
Summer	Report on **FDA 510(k) reform**	Institute of Medicine
2H11	**Abbott's RX Acculink** carotid stent	FDA final decision expected
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
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 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	
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*)
April 30	**Vivus' avanafil** for erectile dysfunction	PDUFA date (*approximate*)
April 30	**Baxter and Halozyme's HyQ** for immunodeficiency	PDUFA date