TRENDS-in-MEDICINE

July 10, 2011

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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

- **Bayer's Nexavar (sorafenib)** – A study published in ***Alimentary Pharmacology and Therapeutics*** showed that combining this drug for advanced renal cell carcinoma with transarterial chemoembolization to treat patients with advanced primary liver cancer was safe and had the potential to improve survival for certain groups of patients.
- **Boston Scientific's Mustang PTA balloon catheter** – The company launched this 0.035" percutaneous transluminal angioplasty (PTA) catheter in the U.S., Europe, and other international markets.
- **Bristol-Myers Squibb's Nulojix (belatacept)** – The Risk Evaluation and Mitigation Strategy (REMS) for this transplant drug was announced, and it points to an increased risk of post-transplant lymphoproliferative disorder (PTLD) predominantly involving the central nervous system and progressive multifocal leukoencephalopathy (PML).
- **Cadence's Ofirmev (IV acetaminophen)** – Only five months after Cadence gained FDA approval for this painkiller, an unidentified generic drug firm is challenging its patent, submitting an abbreviated new drug application (ANDA) with the FDA.
- **Cadila Healthcare** – The FDA sent the company a warning letter saying that it violated manufacturing practice rules at one of its plants in India, which makes generic injectable drugs.
- **Cardiac stents** – A study published in the ***Journal of the American Medical Association*** found that one in nine non-emergency angioplasties may be inappropriate. Researchers, looking at data collected by the American College of Cardiology on ~500,000 angioplasties performed in 2009 and 2010, found that nearly 99% of emergency angioplasties were appropriate, but only half of the elective cases definitively met the criteria, and nearly 12% were inappropriate.
- **CytRx's INNO-206** – The FDA granted orphan drug status for this tumor-targeted doxorubicin conjugate for soft tissue sarcoma. The company said it will begin a Phase IIb trial for the drug, which it said can deliver a four times higher dose of the chemotherapy drug doxorubicin vs. the standard dose.
- **Dr. Reddy's Laboratories** – The FDA banned drugs made at the company's Mexican plant for violation of current good manufacturing practices (CGMP).
- **Epilepsy drug bioavailability** – A study published in ***Annals of Neurology*** found that the bioavailability of generic epilepsy drugs was generally similar to branded drugs,

but not as much when supposedly bioequivalent drugs were compared to each other. Pharmacokinetic (PK) data submitted to the FDA for 141 generic anticonvulsants showed that switching between products containing the same active ingredient led to differences of ≥15% in maximal serum concentrations almost 40% of the time.

- **EXELIXIS' cabozantinib** – The company will take about three months longer than expected to report top-line data from the Phase III EXAM trial of this medullary thyroid cancer drug. The results are now not expected until 4Q11. Exelixis said it needs more time to reach a pre-specified number of events.

- **MERCK KGAA and IDERA PHARMACEUTICALS' IMO-2055** – Merck abandoned development of this head and neck cancer drug due to adverse events, including blood cell abnormalities. Idera said it intends to complete a Phase II trial that is under way and that its collaboration with Merck will continue.

- **MICELL TECHNOLOGIES' MiStent drug-eluting coronary stent system** – The company said it is reducing the sample size in its ongoing, multicenter DESSOLVE-II CE Mark study from 270 to 171 patients with documented or undocumented stable or unstable angina pectoris, based on the results of the four-month follow-up of the first 10 patients.

- **NATIONAL CREATIVE ENTERPRISES' batteries** – The FDA sent the company a warning letter saying its response to complaints about its medical device replacement batteries was inadequate, that quality control was lacking, and that the company had failed to provide a full annual device listing to the FDA since 2008.

- **PFO closure** – A ***CRTonline*** survey on the future of patent foramen ovale (PFO) closure found that 61% of doctors believe the procedure has no future, 33% said it will be used primarily for stroke prevention, and 6% said it will be used primarily for treatment of migraine headaches.

- **PHARMASSET's PSI-7977 and JOHNSON & JOHNSON's TMC-435** will be combined in a Phase II clinical trial in hepatitis C set to begin later this year in patients who have not been helped by standard treatments.

- **Psych drugs** – Three psychiatrists – Joseph Biederman, MD; Thomas Spencer, MD; and Timothy Wilens, MD – were sanctioned by Harvard Medical School and Massachusetts General Hospital for accepting more than $4.2 million from drug companies for psychiatric research and other activities between 2000-2007 without reporting the income, but they weren't fired.

- **RIB-X and SANOFI** plan to co-develop a line of experimental antibiotic therapies. Sanofi will have the option to license Rib-X's RX-04 antibacterial drugs.

- **Russian police raid pharmas** – Russian police searched the offices of four pharmaceutical companies in Moscow, including **Novartis** and **Teva**, as part of an alleged carve-up of the market for supplying the state healthcare system with essential drugs.

- **SANOFI's Multaq (dronedarone)** – The Phase IIIb PALLAS trial in patients with permanent atrial fibrillation (AFib) was stopped early because of increased cardiovascular events in patients. *It wouldn't be surprising to see the FDA open a review now.*

- **SSRIs** – Pregnant women who take selective serotonin reuptake inhibitor (SSRI) antidepressants may have an increased risk of having a child with autism, according to a study published in the ***Archives of General Psychiatry***. Researchers using the Kaiser Permanente database found that fetuses exposed to SSRIs had a 2.2-fold increased risk of an autism spectrum diagnosis (ASD) and that first-trimester exposure increased the risk 3.8-fold.

- **Stem cells** – Scientists at Toronto's University Health Network isolated a rare type of stem cell that can regenerate all the types of cells in the blood system, according to a story published in ***Science***.

- **Sudden cardiac death** – A gene associated with sudden cardiac death has been identified. A meta-analysis of five genome-wide association studies identified a genomic host spot called the BAZ2B locus, which doubles the risk of sudden cardiac arrest.

- **Teleradiology** – Rajashakher Reddy, MD, founder of teleradiology services provider **Reddy Solutions**, was found guilty of 29 counts of fraud related to "ghosting" activities – allowing radiology reports to be approved without actually reviewing the images.

- **THORATEC's HeartMate II LVADs** – A study published in the ***Journal of the American College of Cardiology*** showed that patients age ≥70 have good functional recovery, survival, and quality of life two years after receiving a left ventricular assist device (LVAD). The study was conducted at Sharp Memorial in San Diego CA, which is a Thoratec training site and at which nearly 130 of the devices have been implanted.

- **ZOLL MEDICAL's AEDs** – The FDA sent Zoll a warning letter saying that an inspection of the company's Chelmsford MA factory found failures to validate the battery life of its Zoll automated external defibrillators (AED). The FDA said

Zoll received 15 complaints of battery depletion before the five-year battery life cycle ended.

NEWS IN BRIEF

AMYLIN and LILLY and ALKERMES' Bydureon (weekly exenatide) – no QT problem

The companies said this weekly injectable diabetes drug passed a key cardiovascular study that was performed after the FDA rejected Bydureon and asked for more cardiac data. Bydureon reportedly did not cause QT prolongation in the 75-patient study comparing it to placebo. The complete results will be presented at a future medical conference and will be submitted for publication. Bydureon is expected to be resubmitted to the FDA in 3Q11.

BAXTER HEALTHCARE – positive stem cell results in angina

A Phase II study published in ***Circulation Research: Journal of the American Heart Association*** found that cardiac injections of a patient's own hematopoietic stem cells helped relieve chest pain in patients with chronic angina. A relatively low dose of CD34-positive stem cells reduced weekly angina episodes to 6.8 vs. 10.9 in patients receiving placebo at six months, and the benefits persisted out to one year along with a substantial boost in exercise capability.

Bisphosphonates – safety to be reviewed by FDA panel

The FDA decided to take questions about the safety of bisphosphonates to a joint meeting of its Reproductive Health Drugs Advisory Committee and its Drug Safety and Risk Management Advisory Committee on September 9, 2011. The drugs – Sanofi and Warner Chilcott's Actonel (risedronate), GlaxoSmithKline and Roche's Boniva (ibandronate), Merck's Fosamax (alendronate), and Novartis' Reclast (zoledronic acid) – have been linked to both atypical fractures of the femur and osteonecrosis of the jaw (ONJ).

Doctor shortage looms – study looks 20 years ahead

A study published in the ***Journal of the American College of Surgeons*** predicted a shortfall in the necessary number of physicians and other advanced medical professionals over the next 20 years. The researchers used data from the American Medical Association, the American Association of Colleges of Nursing, the Physician Assistant Education Association, and others to project the future supply of practitioners. They then contrasted these figures with separate projections of demand based on expectations of expenditures made by the Centers for Medicare and Medicaid Services (CMS), the President's Council of Economic Advisors, and the Congressional Budget Office (CBO).

Lead researcher Richard Cooper, MD, from the University of Pennsylvania, said, "More than two-thirds of advanced clinicians are physicians, and…the U.S. is training fewer physicians per capita each year." He estimated that the physician shortage has increased about 1% annually and is now 7%-8% nationally but varies geographically.

The researchers predicted that the current shortages will grow to 20% by 2025 if physician training programs are not expanded. Because of the long lead times to train physicians, adding even 500 additional entry-level positions annually will decrease the future shortages by only a few percent. Adding 1,000 more entry-level positions annually will still leave shortages of 14%-15% in 2025.

Down syndrome – linked to Alzheimer's

A study published in ***Archives of Neurology*** found that people with Down syndrome carry an extra copy of the beta amyloid precursor gene APP, have a heightened risk of Alzheimer's disease, and typically show Alzheimer's disease pathology at autopsy. PET scans from 19 people with Down syndrome were compared to scans from 10 middle-aged controls and 10 elderly people with Alzheimer's disease, and they showed that middle-aged Down syndrome brains had comparable deposits of the ligand [18F] FDDNP, which binds to both beta amyloid and tau deposits. The number of deposits correlated with the participants' ages.

JOHNSON & JOHNSON

- **Natrecor (nesiritide)** – A large randomized trial found that the drug had no significant effect on dyspnea or on the rate of heart failure hospitalization or death at 30 days compared to placebo in patients with acute failure. Also, it leads to increased rates of potentially dangerous low blood pressure, according to a study published in the ***New England Journal of Medicine***.
- **Weekly recall: More Tylenol (acetaminophen)** – The company is recalling 60,912 bottles (one product lot) of Tylenol extra-strength caplets, 225-count bottles, in the U.S. due to the same musty, moldy odor that has been plaguing this and other products.

MERCK

- **Atacicept** – The results of two international trials, published in ***Arthritis and Rheumatism***, failed to show clinical efficacy of **Merck Serono**'s B-cell inhibitor vs. placebo and vs. **Abbott's Humira** (adalimumab).
- **Gardasil, Zolinza (vorinostat), and Cubicin (daptomycin)** – Japanese regulators cleared the vaccine Gardasil for cervical cancer, Zolinza for the treatment of cutaneous T-cell lymphoma, and the antibiotic Cubicin for severe skin and bloodstream infections.

NOVARTIS

- **Afinitor (everolimus)** – A Phase III trial of Afinitor in advanced breast cancer patients was stopped after an interim analysis showed that the study's primary endpoint – a significant difference in progression-free survival vs. control after six weeks – was met. The drug, which is approved to treat several other cancers in the U.S. and Europe, works by blocking a protein that helps tumors grow. The study looked at Afinitor combined with **Pfizer's Aromasin** (exemestane), an aromatase inhibitor, vs. exemestane + placebo. The company said it plans to file for regulatory approval in breast cancer by the end of this year.
- **Arcapta Neohaler (indacaterol maleate)** – The FDA approved the 75 mcg dose of this once-daily inhaled therapy for chronic obstructive pulmonary disease (COPD). The drug, which relaxes muscles around lung airways, is a new molecular entity in the beta$_2$-adrenergic agonist class.
- **Menveo vaccine** – The FDA said promotional material about the meningitis vaccine falsely implied that the product's approved use is consistent with Centers for Disease Control and Prevention (CDC) recommendations. Novartis stopped disseminating the phone script and slides.

NSAIDs – associated with atrial fibrillation

Non-selective non-steroidal anti-inflammatory drugs (NSAIDs) were tied to a 17% increased risk of atrial fibrillation/flutter, according to a study published in the ***British Medical Journal***. Use of COX-2 inhibitors was associated with a slightly higher risk of AFib. There was an increased risk of AFib/flutter of 46% and 71% for those filing new prescriptions for an NSAID or COX-2 inhibitor, respectively.

Obesity – research discovery

New research by the National Institutes of Health (NIH), published in the journal ***Cell Metabolism***, suggests it might be possible to turn fat into muscle, at least in mice. Researchers at NIH's National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) discovered a process (limiting TGF-beta) that turned energy-storing white fat in mice into energy-burning, muscle-like brown fat. The surprising results offer a new avenue of research for obesity treatments.

PFIZER'S Chantix (varenicline) – linked to cardiovascular disease

A study published in the ***Canadian Medical Association Journal*** found that this anti-smoking drug was linked to an increased risk of heart attacks, strokes, and related cardiovascular disease. Researchers who reviewed 14 random, blinded, placebo-controlled trials of Chantix found a 72% increase in heart-related disease in smokers taking the drug vs. placebo. Researchers found that 52 out of 4,908 people taking Chantix had serious cardiovascular events, a rate of 1.06% vs. 0.82% with placebo. While the absolute difference was only 0.24%, the weighted, relative difference was 72%.

The FDA and Pfizer said they will conduct a joint analysis of the Chantix clinical trials. Chantix has been prescribed to ≥13 million smokers. Principal investigator Curt Furberg, MD, PhD, of Wake Forest University called for removal of the drug from the market.

ROCHE

- **Accu-Chek Performa Strip** – These test strips for monitoring blood glucose levels are being recalled in France because errors may occur, causing falsely elevated results.
- **Tarceva (erlotinib)** – Preliminary trial results showed that patients with non-small cell lung cancer (NSCLC) had better outcomes with Tarceva than platinum-based chemotherapy. About 55% of patients responded to Tarceva vs. ~11% with chemotherapy. PFS with Tarceva was 9.4 months vs. 5.2 months for chemotherapy, and median survival was 4.1 months longer with Tarceva.

REGULATORY NEWS

CMS changes diagnostic imaging reimbursement

CMS said that all non-hospital providers of advanced diagnostic imaging, including nuclear medicine, MR, CT, and PET, must obtain accreditation as a condition for reimbursement by January 1, 2012.

CMS flipflops on anemia drugs

CMS proposed ending a rule that a dialysis patient's hemoglobin be maintained >10 g/dL. Just last month, CMS said it had no plans to change reimbursement rules for anemia drugs.

CMS proposes to cut Medicare pay to doctors by 30%

CMS plans to cut doctors' Medicare fees by 30% starting in 2012 in its proposed changes to the 2012 Medicare Physician Fee Schedule. *Similar cuts have been averted almost every year by last-minute congressional reprieve.*

FDA issues draft 510(k) guidance

The FDA issued draft guidance on a proposal to "downclassify" and exempt some Class II devices from the 510(k) requirements. These are devices the Agency believes have well-established safety and effectiveness and controlled risks. Among the devices included in the revision are: collimators, film cassettes, film processors, and digitizers. These devices would no longer have to go through the 510(k) process provided they don't exceed the limitations on exemptions specified in the device classification regulations. The draft guidance is open for comment for 90 days.

FDA 2011 drug approvals likely to surpass last year

The FDA approved 21 new drugs in 2010, and so far this year the Agency has approved 20, so the Agency's 2011 total is likely to be higher than last year's, according to Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research (CDER).

FDA asked to clarify off-label drug use

Seven pharmas – **Allergan**, **Lilly**, **Johnson & Johnson**, **Novartis**, **Novo Nordisk**, **Pfizer**, and **Sanofi** – wrote the FDA, asking the Agency to clarify what it considers off-label drug use – what pharmas can and can't say. The pharmas want details on what's legal, saying current FDA rules are murky and precarious.

FDA's chief counsel leaving

Ralph Tyler is quitting the Agency effective August 5, 2011. A replacement has not been named.

European sterilization standards

The European Committee for Standardization (CEN) updated hospital sterilization standards.

FDA approvals/clearances

- **FUTURE PATH MEDICAL's iBag System** – a disposable urine bag monitored with wireless technology received 510(k) clearance.
- **GLAXOSMITHKLINE's Boostrix** – the first triple combination vaccine for tetanus, diphtheria, and pertussis (whooping cough) in age ≥65.
- **MESOBLAST's "off-the-shelf" mesenchymal precursor cells (MPCs)** – for blood cancer patients who are unable to find donors. The company received approval to begin a Phase III trial of its bone marrow stem cell treatment.
- **SAGENT AND STRIDES ARCOLAB's polymyxin B sulfate** – to treat urinary tract, meninges, and bloodstream infections caused by *Pseudomonas aeruginosa*.

FDA recalls

Each month the FDA issues a report on its recalls, which sometimes contain items that were not announced earlier. Major recalls are often listed in Short Takes or News in Brief, but this also may be of some interest to ***Quick Takes*** readers:

CHURCHILL MEDICAL SYSTEMS' (Vygon) Skin-Prep Wipes and Peripherally Inserted Central Catheter (PICC) insertion trays – due to the potential for bacterial contamination.

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 14	**Seattle Genetics and Takeda's Adcetris** (brentuximab vedotin) to treat both relapsed/refractory Hodgkin's lymphoma and relapsed/refractory systemic anaplastic large cell lymphoma	FDA's Oncologic Drugs Advisory Committee
July 19	**Bristol-Myers Squibb and AstraZeneca's dapagliflozin,** the first SGLT2 inhibitor for Type 2 diabetes	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
July 20	**Edwards Lifesciences' Sapien** percutaneous aortic valve	FDA's Circulatory System Advisory Committee
July 20	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
July 20	**Unnamed gastroenterology drug:** Closed discussion and review	Joint meeting of the FDA's Gastrointestinal Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee
July 21	A humanitarian device exemption for **Berlin Heart's EXCOR pediatric ventricular assist device (VAD)** as a bridge-to-transplant	Circulatory Systems Devices Advisory Committee
	August 2011	
August 12	**Physician-owned distributorships (PODs)**	Inspector General initial report due to Senate Finance Committee
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 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 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
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 Gel** (oxybutinin 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*)