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

- **128-slice CT –** A study published in ***Circulation: Heart Failure*** found that 128-slice CT reduced radiation exposure and accurately detected both MIs and coronary stenosis.
- **ALLERGAN's Botox (onabotulinumtoxinA) –** The FDA approved Botox to treat urinary incontinence in people with neurologic conditions, such as spinal cord injury or multiple sclerosis, who also have overactive bladder.
- **Anti-nerve growth factors (anti-NGFs) –** The FDA postponed its planned Arthritis Advisory Committee meeting scheduled for September 13, 2011. The FDA said it recently received submissions from some of the investigational new drug (IND) application holders that contain "large quantities of new information that will require additional time for Agency review" prior to the advisory committee meeting. No new date for the panel has been set yet.
- **Aromatase inhibitors –** A meta-analysis published in the ***Journal of the National Cancer Institute*** found that there was a trend toward increased mortality with five years of aromatase inhibitor therapy vs. either five years of tamoxifen or a switching strategy.
- **ASTRAZENECA's olaparib –** Data from a 91-patient, open-label Phase II trial, published in ***The Lancet***, showed that 41% of advanced ovarian cancer patients with BRCA1/2 mutations and 24% of non-mutation patients had an objective response to monotherapy with this PARP inhibitor. However, women with BRCA-deficient breast cancer did not respond to the drug.
- **BAYER and ALGETA's Alpharadin (radium-233 chloride) –** The FDA granted fast track status for this therapy for prostate cancer that has metastasized to the bone.
- **CATALENT PHARMA SOLUTIONS** is buying **Aptuit**'s clinical trial supplies business.
- **CORCEPT THERAPEUTICS' Corlux (mifepristone) –** The FDA decided an advisory committee meeting is not needed prior to making a decision on this drug to treat Cushing's syndrome. The PDUFA date is February 17, 2012.
- **DELOITTE** bought most of the assets of **Intrasphere Technologies**, a global drug safety and regulatory consulting business.
- **Flu vaccine –** In a study published in the ***Annals of Neurology***, Stanford researchers reported that winter airway infections such as influenza A (including H1N1) and/or *Streptococcus pyogenes* are triggers for narcolepsy, not flu vaccines.

- **FOREST LABORATORIES' Celexa (citalopram)** – The FDA warned doctors and patients that doses of this SSRI antidepressant >40 mg/day should no longer be used due to both the risk of cardiac arrhythmias and a lack of therapeutic benefit at higher doses.

- **GE HEALTHCARE** is acquiring **PAA Laboratories GmbH**, which focuses on cell biology research, recombinant proteins, antibodies, and vaccines.

- **HEALTHWAYS**, a wellness program operator, is acquiring **Navvis & Co.**, which advises health systems on organization, strategy, partnerships, physician alignment, and service and facility development.

- **HUMANA** is buying **Arcadian Management Services**, an HMO that operates Medicare Advantage plans in 15 states.

- **JOHNSON & JOHNSON's Nucynta ER (tapentadol)** was approved by the FDA for the management of moderate-to-severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. This is the tamper-resistant formulation developed by **Grünenthal**.

- **Metal-on-metal hip implants** – A ***New York Times*** analysis of FDA data found that >5,000 adverse event reports have been made about these devices since January 2011. In May 2011 the FDA ordered the companies to conduct studies to determine failure rates and risks, but a lack of patient registries reportedly is making enrollment difficult.

- **OMNICARE** made an offer to buy **PharMerica**, a pharmacy management services company.

- **PAR PHARMACEUTICAL COMPANIES** is buying rival **Anchen Pharmaceuticals**.

- **PEREGRINE PHARMACEUTICALS' bavituximab** – The company said that a 46-patient Phase II trial found that combining bavituximab, a first-in-class phosphatidylserine (PS)-targeting monoclonal antibody, with **Sanofi's Taxotere** (docetaxel) extended median survival to 20.7 months in patients with advanced breast cancer.

- **PFIZER's Xalkori (crizotinib)** was approved by the FDA to treat patients with late-stage (locally advanced or metastatic) ALK-positive non-small cell lung cancer. In addition, the FDA approved a companion diagnostic test, **Abbott's Vysis ALK Break Apart FISH Probe Kit**, to help determine if a patient is ALK+.

- **PHARMASSET's PSI-938**, an oral guanosine nucleotide analog polymerase inhibitor for hepatitis C, was granted fast track status by the FDA.

- **PLURISTEM THERAPEUTICS' PLX cells**, a treatment for Buerger's disease (a rare condition attacking blood vessels of the limbs), was granted orphan drug status by the FDA.

- **Psoriasis** – A meta-analysis of 22 studies, published in the ***Journal of the American Medical Association***, found that biologic therapies for psoriasis do not significantly increase the risk of cardiovascular adverse events vs. placebo.

- **QRXPHARMA LIMITED's MoxDuo IR (morphine + oxycodone immediate-release)** – The company made a 505(b)(2) submission to the FDA for this painkiller.

- **Radiology** – The U.S. Joint Commission issued an alert on the dangers of medical radiation, which should be a warning to imaging centers that they should be sure their procedures for protecting patients from unnecessary radiation are formalized.

- **RECKITT BENCKISER PHARMACEUTICALS' Nurofen Plus** – U.K. patients initially were warned to be careful using this painkiller because some packages contain an antipsychotic, **AstraZeneca's Seroquel** (quetiapine), instead, but then a total recall was ordered. It is possible the mix-up, which is believed to have occurred at the wholesaler level, was tampering and not a manufacturing issue, and Scotland Yard is investigating.

- **SHIRE's Firazyr (icatibant)** was approved by the FDA for the self-injection treatment of acute attacks of hereditary angioedema (HAE) in people ages 18 years and older. The FDA is requiring that patients be counseled about injection instructions and potential adverse events.

- **TEARSCIENCE's LipiFlow** – The FDA has decided that eyelid thermal pulsation devices like this one for dry eye are Class II devices. This means they can be approved with a PMA but without any clinical trials.

- **Transvaginal mesh** – Public Citizen filed a Citizen Petition with the FDA asking that all surgical mesh products made of non-absorbable synthetic material that are used during transvaginal surgery to repair pelvic organ prolapse (POP) be recalled, further sales be banned, and future versions be classified as Class III medical devices. Public Citizen claimed the mesh offers "no significant benefits but exposes patients to serious risks and the potential for permanent life-altering harm." The FDA will consider issues related to transvaginal mesh products at a two-day advisory committee meeting September 8-9, 2011.

- **UNITED THERAPEUTICS' oral treprostinil** – The drug failed to show a significant improvement in walk distance in preliminary results from a Phase III trial in pulmonary arterial hypertension. However, the company reportedly still plans to try to gain FDA approval.
- **Vaccines** – After a "comprehensive review," the Institute of Medicine (IOM) concluded that common childhood immunizations do not cause chronic diseases such as autism and diabetes.
- **ZIMMER** is permanently closing its surgical products plant in Statesville, NC.

NEWS IN BRIEF

ICDs/pacemakers – infection risk increasing

A 16-year retrospective study published in the ***Journal of the American College of Cardiology*** found that patients who get cardiac electrophysiological devices (e.g., ICDs and pacemakers) are at greater risk of contracting an infection sometime during the lifespan of the device today than they were in the past. Researchers speculated that the increase in infections is due to more use of the devices in patients with comorbidities. Researchers reviewed records for >4.2 million devices and found the incidence of infection increased 210% between 1993 and 2008, from 2,660 cases to 8,230 cases.

NOVARTIS' Tasigna (nilotinib) – beat Gleevec in long-term data

Tasigna, a second-generation tyrosine kinase inhibitor, beat Novartis' own Gleevec (imatinib) at two years in the ENESTnd trial in chronic myeloid leukemia (CML). The results, published in ***The Lancet***, showed efficacy, safety, and tolerability were all better with Tasigna than with Gleevec. Among the findings:

- Up to 71% of Tasigna patients vs. 44% of Gleevec patients had a major molecular response ($p<0.0001$).
- Significantly fewer Tasigna patients progressed to accelerated or blast phase on treatment (2 at low-dose, 5 at high-dose) vs. Gleevec (17).
- Overall survival was comparable.
- The incidence of non-hematological adverse events was comparable.
- Grade 3 neutropenia was less with Tasigna (11%-12% vs. 21%).

PPIs – Public Citizen wants a warning label

Public Citizen asked the FDA to put a boxed warning on proton pump inhibitors (PPIs) – e.g., **AstraZeneca's Nexium** – that these acid reflux therapies can be habit-forming and can lead to other problems, including rebound acid hypersecretion, severe magnesium deficiencies, fractures, and interference with cardiac medications and some cancer chemotherapies.

REGULATORY NEWS

CMS expanding competitive bidding for DME

CMS announced a second round of its competitive bidding program to set prices for durable medical equipment (DME) products such as wheelchairs, oxygen supplies, and hospital beds, moving from the initial nine cities to 91 metropolitan areas. However, **Apria**, **Lincare**, and **Invacare** are predicting that the DME program will cause business closings and create access issues for Medicare beneficiaries.

HHS announces new CMS bundled care program

Calling it an **Affordable Care Act initiative**, the U.S. Department of Health and Human Services (HHS) announced an initiative designed to lower costs while helping doctors and hospitals coordinate care for patients while they are in the hospital and after they are discharged.

The new program, called the Bundled Payments for Care Improvement initiative (Bundled Payments initiative), will align payments for services delivered across an episode of care, such as heart bypass or hip replacement, rather than pay for services separately. The government hopes bundled payments will give doctors and hospitals new incentives to coordinate care, improve the quality of care, and reduce Medicare costs.

Instead of paying hospitals, physicians, and other clinicians who provide care for Medicare beneficiaries, the Centers for Medicare and Medicaid Services (CMS) will bundle care for a "package" of services patients receive to treat a specific medical condition during a single hospital stay and/or recovery from that stay (an episode of care). Providers will have flexibility to determine which services and episodes of care will be bundled together.

NIH finalizes conflict-of-interest rules

The National Institutes of Health issued final rules on financial conflicts of interests for federally funded researchers who also receive payments or stock from drug and medical device

companies. The new regulations require researchers who receive ≥$5,000 from a pharma or device company to disclose this, but institutions will not be required to post the information online. The rules, which will affect ~2,000 institutions and ~38,000 scientists, also include payments to a researcher's immediate family.

European approvals

- **BOEHRINGER INGELHEIM and LILLY's Trajenta (linagliptin)** to treat Type 2 diabetes. It is approved in the U.S. as Tradjenta.
- **CVRX's Barostim neo**, an advanced version of Rheos, an implantable device to lower blood pressure.

FDA approvals/clearances

- **ABBOTT's Vysis CLL FISH Probe Kit** to detect chronic lymphocytic leukemia (CLL) by looking for genetic irregularities in patients' lymphocytes.
- **HEMCON MEDICAL TECHNOLOGIES' GuardaCareXR Surgical**, a gauze dressing coated with chitosan, a shrimp-derived blood-clotting agent, and an X-ray-blocking element that is designed to stop uncontrolled surgical bleeding.
- **JOHNSON & JOHNSON/DEPUY ORTHOPAEDICS' Trumatch** received 510(k) clearance in combination with J&J's Sigma fixed-bearing knee implant.
- **NEC DISPLAY SOLUTIONS' MultiSync MD215MG** – a medical diagnostic display for displaying and viewing of digital mammography images.
- **TEM SYSTEMS' Rotem**, a hemostasis analyzer, received 510(k) clearance.
- **TOPCON MEDICAL LASER SYSTEMS' Pascal Streamline 577**, a 577 nm yellow laser for ophthalmic surgery, received 510(k) clearance.

FDA recalls

- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran) 75 mg** – for an incorrect bar code.
- **TEVA's metronidazole** – for failure to conform with weight specifications.

FDA warning letters

- **DANAHER/BECKMAN COULTER** – for inadequate quality controls in a California plant.
- **GYN DISPOSABLES' IUD Insertion Kits and Endometrial Biopsy Kits** – for failure to comply with cGMP. The FDA also said the company's responses to the violations have been inadequate.
- **TCA CELLULAR THERAPY** – for improper clinical trial conduct, including studies related to several specific stem cell therapies.

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 30	**Silicone breast implant postmarketing and long-term safety issues**	FDA's General and Plastic Surgery Devices Advisory Committee
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 – **postponed indefinitely**
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 20	**Overview of the research program** in the Laboratory of Enteric and Sexually Transmitted Diseases, Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research (CBER), FDA	FDA's Vaccines and Related Biological Products Advisory Committee meeting at NIH ***via teleconference***
September 26-27	**Tissue adhesive materials**	FDA workshop on facilitating innovation in these products
September 30	Institute of Medicine's recommendations for FDA's reform of the **510(k) device clearance program**	Public comment deadline
	October 2011	
October 12	**FDA guidance on diagnostic tests** being developed simultaneously with a drug/biologic	New deadline for industry comment
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 ER), 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 5	**Johnson & Johnson's Xarelto** (rivaroxaban) for stroke prevention in atrial fibrillation	PDUFA date
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 FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
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 26	**Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in prostate cancer	PDUFA date
April 30	**Vivus' avanafil** for erectile dysfunction	PDUFA date (*approximate*)
April 30	**Baxter and Halozyme's HyQ** for immunodeficiency	PDUFA date