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

- **Acetaminophen infant drops** – **Johnson & Johnson/McNeil Consumer Healthcare**, **Novartis**, and **Perrigo** are phasing out infant versions of drugs containing acetaminophen. In an attempt to reduce drug overdoses, they will offer a single formula of these drugs for infants and children. On May 17 and 18, the FDA's Pediatric Advisory Committee and the FDA's Non-Prescription Drugs Advisory Committee will meet jointly to discuss pediatric and over-the-counter use of acetaminophen.
- **BOEHRINGER INGELHEIM PHARMACEUTICALS and LILLY's Tradjenta (linagliptin)**, a DPP-4 inhibitor, was approved by the FDA to improve blood glucose control in adults with Type 2 diabetes. The FDA said it should not be used in Type 1 diabetics or in patients with diabetic ketoacidosis.
- **BRISTOL-MYERS SQUIBB's Coumadin (warfarin)** – The company notified the FDA it was recalling one lot of this blood thinner (5 mg) after finding a tablet that was more potent than it should be.
- **CELL THERAPEUTICS' pixantrone** – The company's appeal of the FDA rejection of this cancer drug was also rejected, but the FDA held out hope for future accelerated approval based on data from one randomized trial if two key matters can be resolved, though the company didn't say what those matters are.
- **DEFIBTECH's DDU-100 series semi-automatic external defibrillators** (all 65,885 of them in the U.S.), sold under the Lifeline AED and ReviveR AED brand names, are being voluntarily recalled because they may inappropriately cancel lifesaving shocks. The FDA classified this as a Class I recall.
- **Drug-eluting stents (DES)** – A letter published in the ***Archives of Internal Medicine*** claimed DES have driven up the cost of healthcare, not only because of their cost but by changing the pattern of care. Peter Groeneveld, MD, from the Philadelphia VA Medical Center and colleagues said DES add $1.57 billion to Medicare expenditures annually.
- **EMERGENT BIOSOLUTIONS** – The federal government extended its contract for anthrax vaccine, and the company plans to create 3.42 million more doses of the vaccine.
- **Generic drugs** – The South Carolina state Senate voted to require the state's Medicaid recipients to try generic drugs to treat cancer, HIV/AIDS, and mental illness if a generic is available. Only if the generic is ineffective will doctors then be able to prescribe a name-brand drug.

- **KERYX BIOPHARMACEUTICALS' Zerenex (ferric citrate)** – The company said it does not expect that European regulators will require additional studies prior to approval of this oral iron for end-stage renal disease (ESRD) patients undergoing dialysis as well as pre-dialysis chronic kidney disease patients. Keryx said it was informed by a European Union (EU) advisory committee that a positive Phase III trial would be sufficient.

- **Levothyroxine** may increase the risk of fractures in elderly patients taking the drug for hypothyroidism, according to a study published in the ***British Medical Journal***. The researchers analyzed data on >200,000 levothyroxine users age ≥70 and found an adjusted odds ratio of fracture of 1.88, with the risk remaining elevated even six months after drug discontinuation.

- **MEDTRONIC** – Senate Finance Committee Chairman Max Baucus (D-MT) sent a letter to Medtronic as part of the committee's investigation into Medtronic's cancellation of five contracts with hospital group purchasing organizations Novation and Premier.

- **Needleless pre-filled glass syringes** – The FDA updated its warning that these syringes have compatibility problems with needleless IV systems, particularly for patients getting adenosine or amiodarone.

- **PROMETHEUS LABORATORIES** bought the U.S. rights to develop Rencarex (girentuximab) from **Wilex AG**. Rencarex is in Phase III development to treat kidney cancer. Wilex also gets the right to sell one of Prometheus' FDA-approved drugs outside the U.S., but it was not announced which drug that is.

- **SEATTLE GENETICS and TAKEDA's brentuximab vedotin** was granted priority review by the FDA for two orphan indications – refractory Hodgkin's lymphoma and anaplastic large cell lymphoma (ALCL). The PDUFA date is August 30, 2011.

- **TARGACEPT's TC-5619** – **AstraZeneca** is not exercising its option to license this potential schizophrenia drug after it failed in a Phase II proof-of-concept study in non-smokers with attention-deficit/hyperactivity disorder (ADHD) despite a positive Phase II study in schizophrenia.

- **TEVA PHARMACEUTICAL INDUSTRIES** outbid Valeant Pharmaceuticals and is buying **Cephalon**. In addition, there is a report that Teva is buying **Taiyo Pharmaceutical Industry**, Japan's third-largest generic drug company.

- **VIVUS's Qnexa (phentermine + topiramate)** – The company said it will resubmit this diet drug in 4Q11 but will ask the FDA only for use in obese people past childbearing age. The company also said it reached agreement with the FDA on objectives for an FDA-requested feasibility study of existing databases to identify past cases of cleft lip in children whose mothers took topiramate during pregnancy.

- **ZELTIA and JOHNSON & JOHNSON's Yondelis (trabectedin)** – Zeltia said its partner, J&J, stopped plans for FDA approval of the combination of Yondelis and Doxil (doxorubicin) to treat women in remission from ovarian cancer after the Agency requested further testing. The potential risks of the combination reportedly outweigh its effectiveness.

NEWS IN BRIEF

ABBOTT LABORATORIES' Kaletra (lopinavir/ritonavir)

- In a study published in the journal ***Antiviral Therapy***, researchers reported cell culture studies found this HIV drug kills cells infected by the human papilloma virus (HPV) while leaving healthy cells relatively unharmed. This suggests lopinavir could be a prevention for cervical cancer. To be effective as an HPV treatment, lopinavir would have to be administered in doses 10-15 times the HIV dose, which would mean putting it in a cream or pessary, not oral administration.

- The company reduced the price for some customers and pointed out it has not raised the price of Kaletra since 2007, while other companies have increased prices on their AIDS drugs 5%-6% annually.

ALLERGAN's Botox (onabotulinumtoxinA) – mutes emotional response

A study published in the journal ***Social Psychology and Personality Science*** found that in addition to removing wrinkles, Botox may remove (or lessen) a person's ability to understand the emotions of others. Researchers at the University of Southern California and Duke University conducted two experiments:

- A 31-patient study of Botox vs. **Medicis**'s Restylane, a dermal filler.

- A 95-patient study of Botox vs. a gel that amplifies muscular signals.

The participants in both experiments viewed computer images of faces and identified the emotions they saw. They found that when the facial muscles were dampened (with Botox), the person had worse emotion perception, and when the facial

muscles were amplified (with the gel), they were better at emotion perception.

Bisphosphonates – more confirmation of atypical fracture risk

A new Swedish study published in the ***New England Journal of Medicine*** found that the use of bisphosphonates increases the risk of rare fractures of the thigh. The study looked at data for 12,777 women age ≥55 and identified 59 women with atypical fractures. They compared these fractures to 263 women who had typical fractures. Using registry data on the use of bisphosphonates, they concluded the rate of atypical subtrochanteric femoral fractures in the general population of older Swedish women ***not*** using bisphosphonates was 0.09 per 10,000 person-years (PY) vs. 5.5 per 10,000 PY for those who took bisphosphonates.

For every 100 days of bisphosphonate use, the risk of an unusual fracture rose by 30%. This means that for one unusual fracture to occur, 2,000 women would have to take a bisphosphonate for one year. However, the risks declined quickly after the drug was stopped.

Brahma (BRM) protein – linked to lung cancer

In two reports published in ***Oncogene***, University of Florida researchers announced their discovery that when variations of the Brahma protein – which is involved in regulation of cellular functions such as gene expression, DNA repair, cell adhesion, and cell division – are too quiet, the risk of lung cancer may increase. When scientists restored the protein to its normal, active self, its cancer-inhibiting properties reappeared. This suggests an alternative anti-cancer approach – promoting or restoring normal cellular processes instead of just inhibiting oncogenes.

Other studies found "silenced" BRM is present in 10%-20% of all solid tumors. The University of Florida researchers found that silencing the BRM gene in a mouse alone did not cause tumor growth, but when carcinogens were introduced, 10 times as many tumors appeared compared with mice with normal BRM expression.

The research also suggests the presence of two polymorphisms within the BRM gene that could potentially be lung cancer biomarkers. The polymorphisms were "greatly enriched" among a group of lung cancer patients tested, and the chance of developing lung cancer with both polymorphisms was 220% higher.

Contrast agents – mixed opinions on black box

The FDA's Cardiovascular and Renal Drugs Advisory Committee, meeting jointly with the FDA's Drug Safety and Risk Management Advisory Committee, couldn't agree on whether the black box on microbubble contrast agents used in echocardiography – **Lantheus Medical Imaging**'s Definity (perflutren lipid microspheres) and **GE Healthcare**'s Optison (perflutren protein-type A microspheres) – is too strict. And, there was no consensus on whether the boxed warning should be removed. The panel basically felt there weren't sufficient new data to answer these questions. The agents are contra-indicated in acute cardiopulmonary syndromes, QT prolongation, severe pulmonary hypertension, and acute decompensated heart failure. The final decision is now up to the FDA.

Vaccine news – polio capsule in development

A University of Central Florida professor received a Gates Grant to develop a cheap polio vaccine in capsule form that can be stored for a year at room temperature, using genetically engineered tobacco and lettuce plants. The associate director for research at the FDA's Center for Biologics Evaluation and Research (CBER), Konstantin Chumakov, PhD, is collaborating on the project and will facilitate advancement of the technology.

REGULATORY NEWS

CMS to expand flu shot access for seniors

CMS plans to issue a rule that would require hospitals, clinics, and other facilities to offer Medicare beneficiaries a flu shot during this fall's flu season. This would mean Medicare beneficiaries would have more options for where to get a flu shot. The providers also would be required to develop policies and procedures for offering flu vaccinations in the case of a future flu pandemic.

FDA reorganizes Office of Antimicrobial Products

The FDA reorganized the OAP "to enhance the logical groupings of therapeutic indications and applications" managed by the review divisions within OAP and to balance their workload. A major focus of this reorganization is the consolidation of oversight of all systemic, non-antiviral, antimicrobial products into one division, instead of having it split between two OAP divisions, to more efficiently address issues of particular concern, such as antibacterial resistance, clinical trial design, and guidance to sponsors of new products and labeling. Edward Cox, MD, remains the director.

The specific changes include:

- The Division of Anti-Infective and Ophthalmology Products (DAIOP) has been renamed the **Division of Anti-Infective Products (DAIP)** and will handle all antimicrobials (including antibacterial, antifungal, and antiparasitic products) except antivirals and certain topical antimicrobials. John Farley, MD, MPH, is the acting director.
- The Division of Special Pathogen and Transplant Products has been renamed the **Division of Transplant and Ophthalmology Products (DTOP)** and will oversee solid organ transplant and ophthalmology products. Renata Albrecht, MD, is the director, and Wiley Chambers, MD, is the deputy director.
- The **Division of Antiviral Products (DAVP)** will remain unchanged. Debra Birnkrant, MD, is the director, and Jeffrey Murray, MD, MPH, is the deputy director.

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

- **Bristol-Myers Squibb**'s Sprycel (dasatinib) and **Novartis**'s Tasigna (nilotinib) – NICE said the National Health Service (NHS) in Britain should not pay for the chronic myeloid leukemia drugs in patients who fail Novartis's Gleevec (imatinib), which is sold in Europe as Glivec, because the benefits of the drugs do not justify the cost. And NICE also rejected higher-dose Gleevec for these patients.

FDA approvals and clearances

- **ABBOTT LABORATORIES' AndroGel** 1.62%, a testosterone gel.
- **D. MEDICAL INDUSTRIES/SPRING-SET HEALTH SOLUTIONS' Spring Universal Infusion Sets** for insulin pumps. The company expects to introduce the product in the U.S. this quarter.
- **MAQUET CARDIOVASCULAR's Cardiohelp** portable heart-lung support system received 510(k) clearance. The company expects to begin commercialization sometime this year.
- **MEDTRONIC's Attain Ability Plus and Attain Ability Straight** – dual-electrode leads that can be used with cardiac resynchronization therapy (CRT) systems.
- **MICROPHAGE's KeyPath MRSA/MSSA Blood Culture Test** – the first test for *Staphylococcus aureus (S. aureus)* infections that is able to quickly (within ~5 hours) identify whether the bacteria are methicillin resistant (MRSA) or methicillin susceptible (MSSA).
- **NOVARTIS's Afinitor (everolimus)** – to treat patients with progressive neuroendocrine tumors located in the pancreas (PNET) that cannot be removed by surgery or that have metastasized. Afinitor is approved and sold as Zortress to prevent organ rejection after a kidney transplant, but the FDA noted that Zortress has a different safety profile in those patients.
- **SECTRA IMTEC's Sectra MicroDose Mammography** – This digital mammography system with high-resolution images was already approved in Europe, Australia, and elsewhere.

European regulatory actions

- **MAZOR ROBOTICS' SpineAssist**, a surgical robotic system to help doctors implant electrodes for deep brain stimulation in patients with Parkinson's disease, depression, etc., received a CE Mark. Earlier this year, Mazor signed distribution agreements with **AB Medica** and **InSpine** to market the device in Italy and the Netherlands.
- **SAVIENT PHARMACEUTICALS' Krystexxa (pegloticase)** – The company has submitted this drug to European regulators as a treatment for chronic gout in patients who do not respond to standard therapy. Krystexxa already has FDA approval.

FDA recall report

The FDA's most recent recall report, which sometimes contain items that were not announced earlier, includes these products and companies that may be of interest to *Quick Takes* readers:

- **PHILIPS MEDICAL SYSTEMS' MX 16-slice CT scanners** – Philips and **Neusoft Medical Systems** (China) recalled 168 CT scanners due to inaccurate dimensions measurements displayed when using the "Combine Viewing" option. If the dimension measurements from merged images created using this option were used, it could result in misdiagnosis.
- **ZIMMER's NexGen Knee** – The company recalled numerous lots of instrumentation for this artificial knee due to the potential for breakdown of the AlTiN PVD (black) coating during surgery. The FDA said the coating could fall into the surgical site. Zimmer received 22 reports of the black coating coming off the instruments after cleaning and sterilization cycles, and five of these delayed surgery.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	May 2011	
May 12	**BioMimetic Therapeutics' Augment Bone Graft**, an alternative to autologous bone grafts (PMA application)	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
May 12	Administration plan for the **prevention and treatment of HCV**	HHS announcement
May 17-18	**PK, safety, and efficacy data plus OTC dosing information and pediatric labeling** for acetaminophen	Joint meeting of the FDA's Non-Prescription Drugs Advisory Committee and Pediatric Advisory Committee
May 19	Discussion of ACCORD Lipid trial as it relates to **Abbott Labs' Trilipix** (fenofibric acid)	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
May 23	**Vertex Pharmaceuticals' telaprevir**, a treatment for hepatitis C	PDUFA date
May 29	**Roche/Genentech's Lucentis** (ranibizumab) – results of Phase III trial	EURETINA Congress in London
May 30	**Optimer Pharmaceuticals' fidaxomicin** for the treatment of *C. diff*	PDUFA date
	June 2011	
June 2-3	Approaches and endpoints for devices for **seizure detection, cognitive evaluation, and traumatic brain injury/concussion assessment**	Joint workshop of the FDA, the American Academy of Neurology, the American Epilepsy Society, and the National Academy of Neuropsychology
June 8-9	**Reprocessing medical devices**	FDA public workshop
June 17	**Celgene's Istodax** (romidepsin) – sDNA for peripheral T-cell lymphoma	PDUFA date
June 17	**Pfizer/King Pharmaceuticals' Acurox** (immediate-release oxycodone), a painkiller	PDUFA date
June 23	**Pfizer/King Pharmaceuticals/Pain Therapeutics' Remoxy** (tamper-resistant oxycodone CR) for pain	PDUFA date
June 23-24	**HCV drug development**	Workshop on Clinical Pharmacology of Hepatitis Therapy, Boston
June 28-29	**Roche/Genentech's Avastin** (bevacizumab), hearing on appeal of FDA's decision to withdraw the indication for metastatic breast cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
June 29	**Cellular and gene therapy products** for retinal disorders	FDA's Cellular Tissue and Gene Therapies Advisory Committee
	Other 2011 meetings/events	
July	**Novartis's Arcapta Neohaler** (indacaterol) long-acting beta agonist (LABA) for COPD	PDUFA date
July 20	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
August 20	**Regeneron's afilbercept** (VEGF Trap-Eye) for AMD	PDUFA date
August 25	**Shire's Firazyr** (icatibant) for hereditary angioedema	PDUFA date
August 30	**Seattle Genetics and Takeda's brentuximab vedotin** for two orphan indications – refractory Hodgkin's lymphoma and anaplastic large cell lymphoma (ALCL)	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 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
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
	2012 meetings/events	
February 2012	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation