TRENDS-in-MEDICINE

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by Lynne Peterson

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…

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SHORT TAKES

- **AMERICAN REGENT's ammonium molybdate injection** – A voluntary recall was initiated due to the presence of particulate matter that could disrupt blood flow within small blood vessels in the lungs and/or cause localized inflammation and granuloma formation.
- **BOSTON SCIENTIFIC's Ion** – This paclitaxel-eluting stent (sold as Taxus Element in Europe) was approved by the FDA, and the company plans to launch it by mid-2012 when **Abbott** stops supplying Boston Scientific with Promus stents.
- **CEPHALON's Provigil (modafinil)** – The European Commission is investigating a 2005 patent settlement between Cephalon and **Teva**. The concern is whether the deal "may have had the object or effect of hindering" introduction of a generic version of this sleep-disorder drug.
- **DAIICHI SANKYO's edoxaban**, a direct Factor Xa inhibitor, was approved by Japan's Ministry of Health, Labor, and Welfare at a daily dose of 15 mg and 30 mg for the prevention of venous thromboembolism after total knee arthroplasty, total hip arthroplasty, and hip fracture surgery.
- **EISAI and TEIKOKU PHARMA's transdermal donepezil** – The FDA rejected this once-weekly transdermal patch version of **Pfizer**'s Aricept.
- **Embryonic stem cell research** – A federal appeals court overturned a judge's ruling last summer that National Institutes of Health funding of embryonic stem cell research violates a law against destroying human embryo.
- **HORIZON PHARMA's Duexis (ibuprofen + the antacid famotidine)** – The company expects to launch this painkiller in 2H11.
- **INSPIRE PHARMACEUTICALS' AzaSite (azithromycin ophthalmic solution)** – The FDA called a four-page ad in a medical journal false and misleading, saying it "broadens the indication, makes unsubstantiated claims, and omits and minimizes important risks." The FDA ordered Inspire not to use this ad.
- **Latex gloves** – Public Citizen petitioned the FDA for the second time to ban latex and cornstarch-powdered gloves, saying they can expose healthcare workers and patients to serious allergic reactions. The Agency proposed adding a warning to the label of these products, but Public Citizen called that "grossly inadequate" and predicted it would have little impact.

- **MEDITHERM's med2000** – The FDA issued a warning letter to the company and to Joseph Mercola, DO, of Chicago suburb Hoffman Estates for promoting this thermography device for unapproved (off-label) diagnostic purposes.
- **ONCOMED PHARMACEUTICALS and BAYER's OMP-18R5** – A Phase I trial of this monoclonal antibody designed to decrease tumor-initiating cells across a variety of tumor types has been cleared by the FDA to begin.
- **Percutaneous aortic valves** – An online survey by ***CRTonline.org*** found that 63% of cardiologists believe the best way to reduce the stroke rate with transcatheter aortic valve replacement is with an embolic protection device, while 21% believe three months of warfarin post-procedure is the solution, and 16% believe alternatives to femoral access are the answer.
- **PFIZER/KING/PAIN THERAPEUTICS' Remoxy (tamper-resistant oxycodone controlled-release)** – A 45-patient study in drug abusers found this painkiller is more difficult to abuse than **Purdue Pharma**'s OxyContin (oxycodone IR and CR) or placebo. Reportedly, the patients did not enjoy Remoxy as much as OxyContin, did not come to like it as quickly, and could not chew it for very long due to the texture and unpleasant taste.
- **REGENERON PHARMACEUTICALS and SANOFI-AVENTIS's Zaltrap (afilbercept or VEGF Trap)** extended survival by ≥20% in combination with chemotherapy in a 1,226-patient Phase III colorectal cancer trial. The companies plan to submit Zaltrap to the FDA in 2011. Zaltrap failed to show a survival benefit in a lung cancer trial earlier this year. *This is a different formulation of afilbercept than that used for age-related macular degeneration (AMD).*
- **ROCHE/GENENTECH's Lucentis (ranibizumab) and Avastin (bevacizumab)** – The CATT trial, sponsored by the National Eye Institute, comparing Avastin and Lucentis head-to-head, found no efficacy difference and no significant safety difference between these two anti-VEGF drugs for wet AMD. (*For more details, watch for the* ***Trends-in-Medicine*** *report from the Association for Research in Vision and Ophthalmology (ARVO) meeting, which will be published in early May.*)
- **SEQUELLA's SQ-109** – In a licensing deal with a Russian venture capital fund, this drug, which was discovered jointly by Sequella and the National Institute of Allergy and Infectious Diseases (NIAID), will be tested in the Russian Federation and neighboring countries as a treatment for tuberculosis.
- **STAAR SURGICAL's Visian Implantable Collamer Lens (ICL)** V4c design received a CE Mark.
- **TEVA PHARMACEUTICALS'** plant in Irvine CA resumed production after resolving manufacturing issues cited by the FDA in a warning letter in 2009.
- **TOSHIBA MEDICAL SYSTEMS** is buying longtime partner **Vital Images**.
- **XENOPORT's arbaclofen placarbil** – The FDA has given permission for the company to start a Phase III trial as a treatment for multiple sclerosis patients with spasticity, and the ~200-patient, 13-week, dose-ranging (15 mg-45 mg) trial is expected to begin in 2Q11.

NEWS IN BRIEF

ABBOTT LABORATORIES' atrasentan – failed in Phase III prostate cancer trial

This endothelin antagonist in combination with docetaxel did not slow disease progression or improve survival better than chemotherapy alone in a Phase III trial in castration-resistant prostate cancer. The National Cancer Institute sponsored the S0421 trial, which was conducted by the SWOG cooperative research group (formerly Southwest Oncology Group). Follow-up for the study was supposed to continue for 36 months but ended at 1.5 years with 1,000 patients enrolled after a planned interim analysis showed "the evidence indicating no benefit from [atrasentan] was strong enough to close the study."

ALKERMES' Vivitrol (extended-release naltrexone) – positive data

A study published in ***The Lancet*** found Vivitrol is safe and effective for treating opioid dependence disorder. Despite a very high dropout rate (47% of Vivitrol patients and 62% of placebo patients), the 250-patient study at 12 Russian sites found that significantly more Vivitrol than placebo patients had urine-screen-confirmed abstinence by the end of the study (90% vs. 35%, p=0.0002).

Angiotensin receptor blockers (ARBs) – maybe there isn't an MI risk

A meta-analysis published in the ***British Medical Journal*** suggested that, contrary to earlier reports, there might not be an increased risk of myocardial infarction (MI) with ARBs. In the pooled analysis of 37 randomized trials of 147,020 patients, ARB use was not associated with increased MI risk vs. either

placebo or active control. However, the researchers did find a lower stroke risk vs. placebo with ARBs, a decrease in heart failure risk, and a decrease in the risk of new-onset diabetes.

CPOE – to blame for medical errors?

A single-institute study at Memorial Sloan-Kettering Cancer Center (MSKCC), published in the ***American Journal of Roentgenology***, found that the majority of "near misses" or "close calls" (errors caught before a patient is harmed) in radiology are repeated errors that carry severe risks for patients. Nearly half of these were detected by simple good fortune, but because injury was prevented, they don't get much attention from risk managers.

The researchers evaluated 62 close calls in radiology at MSKCC between 2007 and 2009 and found that 65% could have caused death or a regulatory breach and 15% were extremely hazardous. The most common errors (32%) came from computerized provider order entry (CPOE), leading the researchers to label CPOE as a "critical vulnerability" attributable mainly to the human/technology interface.

Hepatitis B virus (HBV) – breakthrough often due to non-adherence

A 148-patient, retrospective study published in the journal ***Hepatology*** found that virologic breakthrough is common in patients on nucleoside analogs (NUCs) for HBV – lamivudine, adefovir, entecavir, telbivudine, and **Gilead Sciences**' Viread (tenofovir). However, the researchers said this was most likely due to non-adherence to the treatment regimen, not antiviral drug resistance.

With a mean follow-up of 38 months, 26% of patients had ≥1 viral breakthrough, but on retesting, 38% of these did not have a viral breakthrough. The probability of a confirmed viral breakthrough at five years was 30%, but nearly 40% of the viral breakthroughs were unrelated to antiviral drug resistance.

INTERMUNE's Esbriet (pirfenidone) – positive data in diabetic nephropathy

This antifibrotic agent may do more than just slow diabetic nephropathy; it may actually improve the condition, according to preliminary research published in the ***Journal of the American Society of Nephrology***. The researchers reported that a 77-patient, double-blind, placebo-controlled study found that kidney function (eGFR) continued to drop in diabetic kidney disease patients without treatment but rose significantly over one year with 1200 mg pirfenidone (up 3.3 ml/min/1.73 m^2 vs. down 2.2 ml/min/1.73 m^2 with placebo, p=0.026). No pirfenidone patients at this dose required dialysis vs. four placebo patients.

Efficacy of pirfenidone at a higher dose (2400 mg) was no better than placebo and had a high dropout rate. Saying additional efficacy data are needed, the FDA rejected pirfenidone last year as a treatment for idiopathic pulmonary fibrosis (IPF).

JOHNSON & JOHNSON

- It's official: J&J is buying **Synthes**.
- **Zytiga (abiraterone) –** J&J subsidiary **Centocor Ortho Biotech**'s drug was approved by the FDA as an oral treatment (in combination with prednisone) for castration-resistant prostate cancer (CRPC) in men who had prior chemotherapy. The company plans to launch it soon at ~$5,000/month with a median 8-month treatment.

LILLY

- **LY-2140023** – The company started a Phase III trial of this atypical antipsychotic for schizophrenia, which is thought to cause less weight gain than approved atypical antipsychotics.
- Will collaborate with **Medtronic** on an implantable drug delivery system to treat Parkinson's disease, combining Medtronic's drug infusion technology (implantable pump) with Lilly's glial cell-derived neurotrophic factor.

PFIZER/KING PHARMACEUTICALS' Altace (ramipril) – very effective in obese patients

Obese patients with kidney disease progress more quickly toward renal failure than non-obese patients, but a study published in the ***Journal of the American Society of Nephrology*** found that Altace abolished that excess risk. Italian researchers analyzed data from a previously completed trial comparing Altace with placebo in 337 patients with chronic kidney disease (CKD) not related to diabetes. On placebo, the risk of developing end-stage renal disease (ESRD) was more than twice as high for obese patients vs. normal-weight patients (24 vs. 10 per 100 person-years). For patients who were overweight but not obese, the ESRD risk was similar to that in normal-weight patients.

Altace lowered the risk of progression to ESRD in all three weight groups. However, the magnitude of risk reduction was much greater for obese patients: 86% vs. 45% for normal-weight patients. Thus, obese patients taking Altace exhibited about the same ESRD risk as normal-weight patients.

PFIZER

- **Aricept (donepezil) – ineffective in MS.** Aricept failed to meet the primary endpoint – improvement in memory impairments – in multiple sclerosis in a placebo-controlled, 6-month, 120-patient, multicenter trial published in ***Neurology***. Neither the patients' impressions of memory function nor their scores on an objective test of verbal memory (the Selective Reminding Test) were better with Aricept, and there were more side effects with Aricept, including more diarrhea, GI problems, and frequent urination. The study was funded by the National Institutes of Health and the National Center for Research Resources.

- **Tofacitinib (formerly tasocitinib) – more positive efficacy data in RA.** Pfizer announced more topline data on this JAK inhibitor for moderate-to-severe rheumatoid arthritis (RA). It met the primary endpoint, reducing signs and symptoms, in two Phase III trials:
  - The 12-month, 717-patient ORAL-Standard trial of patients with inadequate response to methotrexate.
  - The 6-month, 399-patient ORAL-Step trial of patients without an adequate response to TNF inhibitors.

  Pfizer said there were no new safety signals, but, once again, it did not provide any clarity on the adverse events of concern.

REGULATORY NEWS

CMS may pay for MRI scans in pacemaker patients

The Centers for Medicare & Medicaid Services (CMS) issued a proposed decision that the evidence is strong enough to reimburse for MRI exams in Medicare patients who have permanent pacemakers that have FDA-approved labeling for use in an MRI environment. Public comment will be accepted until May 25. *If this rule goes into effect, it would be good news for Medtronic's Revo MRI SureScan pacemaker.*

CMS urged to ease telemedicine restrictions for ACOs

In a letter to CMS Administrator Donald Berwick, MD, the American Telemedicine Association (ATA) urged the Agency to eliminate Medicare's "outdated restrictions" on telemedicine, saying they will hamper efforts by accountable care organizations (ACOs) to provide telehealth services under Medicare Parts A and B. ATA said Kathleen Sebelius, secretary of the Department of Health and Human Services (HHS), has the legislative authority to waive the telemedicine restrictions but didn't do that in the proposed ACO rulemaking.

CMS to pay hospitals bonuses for quality adherence

CMS released the Hospital Value-Based Purchasing Program rule, which goes into effect in October 2012. Under the new rule, CMS will pay hospitals bonuses for improvements in patient health, rather than for the number of services received during a hospital stay. CMS administrator Dr. Berwick, "For the first time, hospitals are going to be paid for inpatient hospital quality, not just the quantity of the care they provide."

In the first year of the program, CMS plans to give out a total of $850 million in bonuses. The money will come from a 1% across-the-board reduction in Medicare payments to hospitals starting in fiscal year (which begins in October 2012). The bonuses will be based on a hospital's performance clinical quality measures, which include things like whether a hospital provided care to heart attack patients within 90 minutes or whether a hospital successfully prevented a patient from developing a blood clot in the first 24 hours after surgery. CMS is weighting the quality care measures at 70% of the decision and patient satisfaction scores at 30%.

In 2015, hospitals that aren't keeping pace with meeting the quality care and patient satisfaction benchmarks will face a cut in reimbursement.

Until now, hospitals were required to report their performance on the quality measures, with a 2% reduction in Medicare payments for lack of reporting. That changes under the new rule, so hospitals' reimbursement will not be based on ***whether*** they're reporting to CMS but on how well they are actually ***complying*** with the measures.

FDA preparing simpler, shorter patient guides

In partnership with the Brookings Institution, the FDA plans to create a new, one-page, standard information document for medications to be called Patient Medical Information (PMI). The FDA does ***not*** plan to review or approve PMI documents, instead relying on industry self-regulation. However, the American Society of Health-System Pharmacists was critical of the lack of FDA oversight of PMIs.

FDA improving instructions for reusable medical devices

The FDA announced steps to help reduce the risk of exposure to improperly reprocessed devices that can lead to the transmission of disease. Reprocessing is a multistep process which includes cleaning, disinfecting, or sterilization to remove debris and biologic materials. The FDA believes some devices present challenges to reprocessing.

Based on premarket and postmarket data on reprocessed devices (e.g., endoscopes), the FDA identified device design features that reduce the likelihood of retaining debris and that facilitate proper reprocessing, including smooth inner surfaces with long, narrow interior channels; clear identification of components that must be discarded after patient use; and designs that take into account how fluid moves through reusable medical devices.

On June 8-9, 2011, the FDA will sponsor a public workshop to discuss these findings and collaborate with representatives from other government agencies, manufacturers, healthcare providers, and other stakeholders on future device design and scientific advances in reprocessing.

The FDA is issuing a draft guidance to provide greater clarity on how to scientifically validate the reprocessing instructions that are part of a device's label, and the Agency is working with standards-setting groups on this. The FDA also developed a webpage for use by healthcare facilities seeking to implement reprocessing quality assurance programs.

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

- **Amgen's Nplate (romiplostim)** – recommended for coverage by the National Health Service (NHS) as a treatment for adults with chronic idiopathic immune thrombocytopenic purpura (ITP).
- **Zeltia's Yondelis (trabectedin)** – rejected for treatment of ovarian cancer. NICE said the company didn't submit evidence comparing Yondelis with platinum-based chemotherapy. Zeltia offered to provide Yondelis free after the fifth cycle of treatment, but NICE said that proposal still didn't make the drug cost-effective because "the benefits aren't clear."

Drugs under FDA safety review

The FDA's quarterly drug safety watch list identifies nine drugs that the Agency said have shown potential signs of serious risks according to its Adverse Event Reporting System (AERS). The FDA is currently studying these drugs to determine if there is enough risk to warrant action – e.g., label change, a risk evaluation and mitigation strategy (REMS), recall, new trial requirement, etc. The new drugs on the watch list are:

- **ASTELLAS' Lexiscan (regadenoson)**, a radionuclide myocardial perfusion imaging agent – for QT prolongation
- **Fenofibrates, cholesterol and triglyceride-lowering agents** – for paradoxical decreases in HDL
- **GENZYME's Renagel (sevelamer)**, a phosphorus binder – for esophageal obstruction
- **JOHNSON & JOHNSON's Simponi (golimumab)**, an anti-diabetic drug – for hypersensitivity reactions and anaphylaxis
- **LUNDBECK's Neoprofen (ibuprofen lysine)**, an NSAID – for serious skin reactions in children
- **MERCK's Saphris (asenapine maleate)**, an atypical antipsychotic – for hypersensitivity reactions
- **PFIZER/KING PHARMACEUTICALS' Embeda (morphine + naltrexone)**, a painkiller – for withdrawal symptoms
- **PURDUE PHARMA's OxyContin (oxycodone)**, a painkiller – for choking and GI obstruction
- **SANOFI-AVENTIS's Multaq (dronedarone)**, an anti-arrhythmic – for liver failure

FDA approvals and clearances

- **ACOUSTICON's ACAM-5 system**, a device to help audiologists assess the severity of hearing loss and better fit hearing aids.
- **BIOMET's Active Articulation E1** – This dual-mobility hip replacement device received 510(k) clearance.
- **MEDICIS' Restylane** – An FDA advisory committee recommended that the FDA expand the label for this dermal filler to include not only facial wrinkles and laugh lines but also plumping up lips.

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 2	**Safety of ultrasound contrast agents**, including new data and status of required postmarketing trials: Lantheus Medical Imaging's perflutren lipid microsphere injectable suspension (NDA); GE Healthcare's perflutren protein-type A microspheres injectable suspension (NDA); and Bracco Diagnostics' sulfur hexafluoride microbubble injection (IND)	FDA's Cardiovascular and Renal Drugs Advisory Committee meeting jointly with the FDA's Drug Safety and Risk Management Advisory Committee
May 4-5	**Biosimilar challenges and opportunities**	Joint DIA and FDLI conference
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
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