TRENDS-in-MEDICINE

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by Lynne Peterson

Quick Takes

…Highlights from this week's news affecting drugs and devices in development that are not covered in longer *Trends-in-Medicine* reports…

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SHORT TAKES

- **COOK's single, double, triple, and 5-lumen central venous catheter trays,** as well as the company's single and double lumen PICC trays, were recalled due to problems with the plunger luer that could cause leakage and loss of sterility.
- **DAIICHI SANKYO** is buying **Plexxikon**, which is co-developing a BRAF inhibitor for metastatic melanoma, PLX-4032.
- **GTx's toremifene –** GTx and **Ipsen** ended their development deal for this therapy designed to reduce bone fractures in men with prostate cancer being treated with androgen deprivation therapy. In 2009, the FDA asked for more information before considering the drug for approval.
- **Implantable cardioverter defibrillators (ICDs) –** A retrospective substudy of the SCD-HeFT trial, published in ***HeartRhythm***, found that ICD implantation is beneficial and safe 40 days after a myocardial infarction (MI), and implantation does not need to be delayed for 18 months.
- **INFINITY PHARMACEUTICALS' IPI-926**, a Hedgehog inhibitor, received orphan drug status from the FDA. The company began another Phase II study vs. placebo to test it in inoperable chondrosarcoma.
- **INSULET's OmniPod** insulin delivery system will be sold and distributed in Canada by **GlaxoSmithKline (GSK)**.
- **INTERMUNE's Esbriet (pirfenidone)** received approval from European regulators to treat idiopathic pulmonary fibrosis. InterMune plans to launch the drug in Germany in September, followed by France, Spain, and Italy in 1H12, and the U.K. and other markets later in 2012. The FDA rejected Esbriet in May 2010, saying another trial was needed.
- **JOHNSON & JOHNSON –** This week's recall was for 104 lots of surgical sutures in the U.K. due to a packaging defect that could compromise the sterility of the products.
- **MELA SCIENCES' MelaFind –** The company amended its PMA for this device to detect melanoma to limit the use of the product to dermatologists, in the hope that this will increase its chances of getting FDA approval.
- **MERCK KGAA's cladribine –** The FDA rejected this oral multiple sclerosis therapy, issuing a complete response letter that said it needed more data on safety and risk:benefit from additional analyses of existing clinical trials and/or additional data from new trials. In September 2010, the company withdrew its application in Europe after a regulatory committee there voted against approval.

- **Opioids** taken just before or in the first months of a pregnancy were found to increase the risk of certain birth defects, especially congenital heart defects. The study by the Centers for Disease Control and Prevention (CDC), published in the ***American Journal of Obstetrics and Gynecology***, also found there is an increased risk of having a baby with spina bifida, hydrocephaly, congenital glaucoma, or gastroschisis.

- **Proton pump inhibitors (PPIs) –** The FDA is warning that long-term use of PPIs may lead to low levels of magnesium, which in turn can result in muscle spasms or seizures, irregular heartbeat, and even an increased risk of *Clostridium difficile* (*C. diff*) diarrhea. And low magnesium cannot be reversed in ~25% of cases with magnesium supplements, requiring discontinuation of the PPI. The FDA suggested that doctors get a baseline serum magnesium before prescribing a long-term PPI.

- **REGENERON PHARMACEUTICALS' Arcalyst (rilonacept)** helped prevent gout flares in a Phase III study. The drug, injected at 80 mg or 160 mg per week over 4 months, decreased gout flares by 72% vs. placebo. Regeneron plans to submit the drug to the FDA in mid-2011.

- **ROCHE/GENENTECH's Avastin (bevacizumab) –** European regulators decided to continue to allow use of Avastin for metastatic breast cancer because of the progression-free survival benefit.

- **SECOND SIGHT MEDICAL PRODUCTS' Argus II Retinal Prosthesis System –** This device to restore some sight to blind patients with retinitis pigmentosa and other forms of advanced retinal degenerative conditions received a CE Mark. The company plans to launch the device in Europe this summer and apply for FDA approval later this year.

- **TAKEDA's Actos (pioglitazone) –** A meta-analysis of 13 trials involving 17,627 patients, published in the journal ***Thorax***, found that patients taking a thiazolidinedione – Actos or **GSK**'s Avandia (rosiglitazone) – may have a 40% increased risk of pneumonia or other lower respiratory tract infections.

- **TARGACEPT and GSK** ended their partnership to develop nicotinic receptor-related treatments for addiction, obesity, and other conditions. Targacept said GSK's changes in its strategic focus in neurosciences led to the end of the collaboration.

NEWS IN BRIEF

AMYLIN PHARMACEUTICALS/LILLY/ALKERMES' Bydureon (exenatide extended-release) – not non-inferior to liraglutide

This weekly injectable for Type 2 diabetes missed the primary endpoint, failing to show non-inferiority, in the 912-patient DURATION-6 trial, a head-to-head study vs. **Novo Nordisk**'s Victoza (liraglutide). At Week 26, Bydureon 2 mg decreased HbA_{1c} by 1.3 points vs. 1.5 points for Victoza 1.8 mg daily. In terms of adverse events, Victoza patients had more GI effects (nausea, vomiting, and diarrhea) while Bydureon patients had more injection-site nodules (10% vs. 1%). The FDA rejected Bydureon in October 2010, asking for more data on potential cardiac arrhythmia effects. The companies plan to submit a response in 2H11.

Breast cancer – nanoparticle approach

Scientists at Queen's University Belfast, Ireland, have shown that they can deliver a gene (iNOS) directly into breast cancer cells, causing them to self-destruct, using a nanoparticle gene transport system called Designer Biomimetic Vector (DBV). The findings were reported in the ***International Journal of Pharmaceutics.*** The gene forces the cancer cells to produce poisonous nitric oxide, which either kills the cells outright or makes them more vulnerable to chemotherapy and radiation. And normal cells are unaffected. The therapy is still about five years away from even a Phase I trial, but the work is interesting. And the researchers plan to turn the nanoparticles into a dried powder that would make transport easy; it would just be reconstituted before use.

Breast cancer implants – plastic surgery website language changed

A webinar on the websites of two plastic surgery medical associations – the American Society of Plastic Surgeons (ASPS) and the American Society for Aesthetic Plastic Surgery (ASAPS) – about the risk of cancer with breast implants was criticized as misleading, and it now has been removed. Public Citizen complained to the FDA about the webinar on February 17, 2011, and just 11 days later, Dr. Jeffrey Shuren, director of the FDA's Center for Devices and Radiological Health, informed Public Citizen that the FDA had reviewed the ASPS/ASAPS webinar, spoke with representatives of both organizations, and the associations planned to remove the webinar from their websites.

CELGENE

- **Revlimid (lenalidomide) and Thalomid (thalidomide)** – The U.S. Attorney for the Central District of California is investigating whether Celgene (a) promoted off-label use of its multiple myeloma therapies and/or (b) made improper payments to doctors related to off-label use of those drugs.
- **Istodax (romidepsin)**, which already is approved to treat cutaneous T-cell lymphoma, was granted priority review status by the FDA for use in patients with peripheral T-cell lymphoma who have undergone prior treatment. The PDUFA date for the expanded use is June 17.

Cold medications
– prescription drugs without FDA approval taken off the market

The FDA ordered about 500 prescription drugs used for treating colds, coughs, and allergies removed from the market because they had never been formally approved by the Agency and contain unapproved ingredients. While the drugs have been linked to only a few relatively minor problems, such as drowsiness and irritability, the FDA is concerned that adverse events may be significantly underreported, particularly in children. These are older drugs that were first marketed before FDA approval was required.

Deborah Autor, director of the FDA's Office of Compliance, Center for Drug Evaluation and Research (CDER), said, "We have taken a lot of steps to try to educate doctors…We believe some doctors are aware and some doctors are unaware [that these drugs are not FDA-approved]. Because they are listed in the Physicians Desk Reference (PDR), may be advertised in medical journals brought to their offices by (drug company) detailers, doctors may not always know [if they are approved or not]. And there are doctors out there that continue to prescribe these drugs."

Flu vaccines
– U.S. government funds new technology

The Department of Health and Human Services (HHS) awarded two contracts for the development of next-generation recombinant influenza vaccines that do not require egg-based technology. The funds are for clinical safety and efficacy studies and to perfect the manufacturing processes. The two companies are:

- **VaxInnate** – which is developing technology that combines proteins from influenza viruses and bacteria to elicit a protective immune response.
- **Novavax** – which is developing a virus-like particle (VLP) vaccine technology using insect cells to express influenza proteins.

GILEAD SCIENCES' Letairis (ambrisentan)
– one boxed warning lifted

The FDA modified the boxed warning for this endothelin receptor antagonist for pulmonary arterial hypertension (PAH). The FDA removed the requirement for monthly liver enzyme tests after clinicial trials and postmarketing reports fround only a low risk of liver injury. The boxed warning on the risk of serious birth defects and the contraindication for use during pregnancy remain in the labeling, and the drug will continue to be available only through a restricted distribution program, LEAP (Letairis Education and Access Program).

Negative pressure wound therapy (NPWT)
– FDA issues second warning

For a second time, the FDA is urging caution in prescribing these systems, but the Agency is not changing the labeling. The FDA received reports of six additional deaths and 97 injuries associated with NPWT units since its first warning in November 2009, bringing the total to 12 deaths and 174 injuries linked to the devices since 2007.

Bleeding was the cause of the most serious adverse events, and more than half of the adverse events were for infections. Non-hospital use also appears to be a factor; more than half of the new adverse event reports were at non-hospital locations.

The FDA said doctors should be aware that the systems are inappropriate for certain wound types and urged them to consider a long list of risk factors before prescribing the therapy.

Before issuing this warning, the FDA actually surveyed an unspecified number of healthcare providers about their experiences with NPWT systems. The FDA said, "Overall, respondents felt that there is a definite benefit to NPWT therapy, regardless of the care setting, and that it is a safe therapy when prescribed and administered appropriately…but [that] patients or lay caregivers should not be administering the therapy because they aren't trained to understand the complexities and intricacies of wound care and also because clinical professionals are needed to monitor and assess the wound in addition to changing the dressing."

Parkinson's disease
– could something as simple as ibuprofen prevent it?

A study, published in the journal ***Neurology***, found that taking ibuprofen two or more times a week reduced the risk of developing Parkinson's disease by 38% but doesn't treat the disease. And it is only ibuprofen that has this effect, not other NSAIDs. These findings came when researchers from Harvard University and the National Institute of Environmental Health Science analyzed data from 136,197 participants in the Nurses' Health Study and the Health Professionals Follow-up Study. Alberto Ascherio, MD, DrPH, the senior author and a Harvard epidemiologist, said, "There is no cure for Parkinson's disease, so the possibility that ibuprofen, an existing and relatively non-toxic drug, could help protect against the disease is captivating." The researchers are calling for a randomized clinical trial to be conducted.

Topiramate
– link confirmed to oral birth defects in children

The FDA announced that new data suggest that topiramate increases the risk for cleft lip and cleft palate in babies born to women taking the drug during pregnancy. The FDA is advising doctors to warn women of childbearing age about this risk before taking it for epilepsy or migraine prophylaxis and to consider alternative medications, but the Agency is not banning the drug.

The FDA action comes after the North American Antiepileptic Drug (AED) Pregnancy Registry found an increased risk of oral clefts in infants exposed to topiramate during the first trimester of pregnancy (a prevalence of 1.4% vs. 0.38% for other anti-epileptic drugs vs. 0.07% in the general non-epileptic population). The FDA said similar data from the United Kingdom Epilepsy and Pregnancy Register supported the North American data.

Topiramate is getting a stronger label and a new MedGuide, and the pregnancy category is being changed to Pregnancy Category D from Category C. *This would seem to be a death knell for **Vivus**'s diet drug Qnexa (topiramate + phentermine).*

REGULATORY NEWS

CMS still says no to MRIs of pacemaker patients

The Centers for Medicare & Medicaid Services (CMS) concluded that the evidence supporting the use of MRI in patients with pacemakers is promising but not convincing. So, CMS will not pay for MRIs in patients with pacemakers – even Medtronic's new MRI-safer pacemaker. However, CMS will reimburse for MRIs in pacemaker patients as part of clinical studies investigating the effects of MRI on patients with pacemakers.

Congressional call for investigation into drug shortages

Sen. Richard Blumenthal (D-CT) asked the U.S. Government Accountability Office (GAO) to investigate the drug shortages that have plagued U.S. hospitals – the causes, how extensive they are, and how they affect patient care. According to the American Society of Health-System Pharmacists, 148 drugs were in short supply in 2010, 157 in 2009, and <50 in 2006.

GOP senators call for ouster of CMS head

In a letter to President Obama, 42 of the 47 Republican senators called for the removal of Donald Berwick, MD, as CMS administrator. They questioned his credentials, citing a lack of experience in health plan operations and insurance regulation, and "his past record of controversial statements."

Dr. Berwick was a "recess appointment," so his tenure expires at the end of 2011 unless the Senate confirms him, and it takes only 41 votes to block that confirmation. *Thus, Dr. Berwick's tenure at CMS may not last long.*

More money for community oncology clinics?

Rep. Ed Whitfield (R-KY) and Rep. Gene Green (D-TX) plan to introduce legislation to increase Medicare drug reimbursement for community oncology clinics – if they can find a way to pay for it. The proposal would exclude certain discounts extended to wholesalers when calculating Medicare reimbursements.

New risk factor for stent thrombosis

An autopsy study by Renu Virmani, MD, of CVPath Institute, published in the ***Journal of the American College of Cardiology***, found that atherosclerosis in the neointima may be a new risk factor for late stent thrombosis. Dr. Virmani and her staff reviewed 299 autopsies with 406 stented lesions – 209 with drug-eluting stents (both **Johnson & Johnson**'s Cypher and **Boston Scientific**'s Taxus) and 197 with bare metal stents.

Stent Thrombosis with DES vs. BMS			
Measurement	**DES**	**BMS**	**p-value**
Cases of stent thrombosis	209	197	---
Neoatherosclerosis	31%	16%	<0.001
Time to neoatherosclerosis	420 days	2,160 days	---
Time to thin-cap fibro-atheroma or plaque rupture	1.5 years	6.1 years	---
Stent-related deaths from thrombosis	20%	4%	<0.001
In-stent restenosis as a cause of death	28%	7%	<0.001
Neoatherosclerosis for stents implanted <2 years	37% Cypher 21% Taxus	---	0.021
Thin-cap fibromas or plaque ruptures	1%	4%	Nss, p=0.17

NICE rejects Lucentis for DME

The U.K. National Institute for Health and Clinical Excellence (NICE) declined to endorse Lucentis (ranibizumab), which is a **Novartis** drug in Europe, for patients with diabetic macular edema (DME), concluding that the drug's benefit does not justify its cost. NICE previously recommended Lucentis coverage for wet age-related macular degeneration (AMD).

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	March 2011	
March 7	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
March 8	**Novartis' Arcapta Neohaler** (indacaterol maleate), a QD bronchodilator for long-term use in COPD	FDA's Pulmonary-Allergy Drugs Advisory Committee
March 8-9	Recommendation on scientific issues concerning direct-to-consumer (DTC) genetic tests that make medical claims	FDA's Molecular and Clinical Genetics Advisory Committee
March 10	**Roche/Genentech's Lucentis** (ranibizumab) Phase III RISE results in DME	The Macula Society meeting
March 10	Risk of **neurodegeneration in pediatric patients** from anesthetic drugs	FDA's Anesthetic and Life Support Drugs Advisory Committee
March 10	**GlaxoSmithKline's Lamictal XR** (lamotrigine extended-release) and discussion of use of historical-controlled trials as a comparator for anticonvulsant monotherapy in epileptic seizures	FDA's Peripheral and Central Nervous System Drugs Advisory Committee
March 10	**Human Genome Sciences/GSK's Benlysta** (belimumab) for lupus	PDUFA date
March 15	Innovative Pathway for medical devices	FDA public hearing
March 16	Preliminary decision on **how to cover ESAs** for kidney disease patients	CMS decision
March 26	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for advanced melanoma	PDUFA date
	April 2011	
April 2	**Novartis's Gleevec** (imatinib) for GIST	PDUFA date
April 5	**Optimer Pharmaceuticals' fidaxomicin** for the treatment of *C. diff*	FDA Anti-Infective Drugs Advisory Committee
April 7	**AstraZeneca's Zactima** (vandetanib) for inoperable medullary thyroid cancer	PDUFA date
April 7-8	**FDA 510(k) reform**	FDA public meeting
April 10	Open forum to discuss statistical issues related to **drug and biologics development and review**	Joint FDA and Drug Information Agency (DIA) Forum
April 12	**NDA for Novartis's Afinitor** (everolimus) and **sNDA for Pfizer's Sutent** (sunitinib) to treat neuroendocrine tumors	FDA's Oncologic Drugs Advisory Committee
April 13	**KV Pharmaceutical/Hologic's Gestiva** (17-alpha hydroxyprogesterone) to prevent premature birth	PDUFA date
April 14-15	**Cardiovascular Safety and Drug Development:** QT, arrhythmias, thrombosis, and bleeding	Joint FDA/DIA meeting
	Other future 2011 meetings/events	
May 23	**Vertex Pharmaceuticals' telaprevir**, a treatment for hepatitis C	PDUFA date
May 30	**Optimer Pharmaceuticals' fidaxomicin** for the treatment of *C. diff*	PDUFA date
June 16	Final decision on **coverage of ESAs** for kidney disease patients	CMS decision
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 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)
July 20	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	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
October 20	**Johnson & Johnson's abiraterone** for metastatic prostate cancer	PDUFA date
December	**Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to complete	Company announcement or medical conference presentation
	2012 meetings/events	
February 2012	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation