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…

Trends-in-Medicine
Stephen Snyder, *Publisher*
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409
Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

SHORT TAKES

- **ACADIA PHARMACEUTICALS** extended its eye drug partnership with **Allergan** through March 2012.
- **AMARIN's AMR-101 –** The results of the Phase III MARINE trial in patients with very high triglycerides (≥500 mg/dL) will be presented at the National Lipid Association meeting in New York May 19-22. The company previously announced that the trial met its primary endpoint for both doses (2 g and 4 g), reducing triglycerides with no statistically significant increase in LDL.
- **BIOTRONIK –** Nevada Gov. Brian Sandoval ordered an investigation of consulting fees Biotronik paid to Las Vegas cardiologists who were consultants to the company. The investigation comes after the ***New York Times*** reported that 95% of the 263 patients getting ICDs and pacemakers at one Las Vegas hospital last year received Biotronik devices.
- **BOSTON SCIENTIFIC's Promus Element –** This platinum chromium everolimus-eluting stent was submitted to the FDA, and the company hopes to get approval and launch it in the U.S. by mid-2012.
- **BRISTOL-MYERS SQUIBB's Yervoy (ipilimumab) –** In what seems like an unusual move, 11 days after approving this new treatment for metastatic melanoma the FDA issued a MedWatch about the Risk Evaluation and Mitigation Strategy (REMS) for Yervoy, reminding doctors to read the boxed warning and prescribing information for Yervoy, including the boxed warning related to severe immune-mediated adverse reactions.
- **Carbapenem class of antibiotics –** Researchers presented findings at the Society for Healthcare Epidemiology of America meeting that overuse of these antibiotics increased dramatically (102%) in the past five years. This compares to a 79% increase in IV vancomycin and a 41% increase in combinations of penicillin with beta-lactamase inhibitors.
- **CUBIST PHARMACEUTICALS' Cubicin (daptomycin)** is being licensed to **Teva Pharmaceutical Industries** to resolve a patent dispute. This means Teva can launch its generic Cubicin on December 24, 2017, unless Cubist gets a six-month pediatric extension.
- **GENZYME's Fabrazyme (agalsidase beta) –** A group of Fabrazyme patients filed a petition with the National Institutes of Health asking for a rehearing of their 2010 petition to have Genzyme's patent on this treatment for their disease set aside, arguing that Genzyme has not been able to meet demand due to production contamination. In December 2010, NIH denied the March-in Petition, saying it would take too long for a

new manufacturer to get necessary approvals to make the drug.

- **HEALTHPOINT's Xenaderm (balsam peru, castor oil, trypsin)** – The Department of Justice filed a False Claims Act complaint against the company for allegedly selling an unapproved wound care drug (for bedsores and pressure sores) and causing Medicare and Medicaid to be fraudulently billed millions of dollars, despite the FDA revoking marketing approval for Xenaderm in the 1970s.
- **MEDTRONIC's InterStim** – This implantable device to electrically stimulate the sacral nerves received a new indication: treatment for chronic fecal incontinence. It was already approved to treat non-obstructive urinary retention and overactive bladder.
- **NEUROVASX' cPAX Aneurysm Treatment System** – The FDA granted humanitarian device status to this treatment for cerebral aneurysms.
- **NOVO NORDISK** patented a synthetic version of an intestinal hormone (PYY) for obesity. The analogues are being investigated as an injectable therapy.
- **Oncology trials** – The National Cancer Institute selected 27 sites to take part in the Cancer Immunotherapy Trials Network, led by the Fred Hutchinson Cancer Research Center to study promising new immunotherapies for cancer.
- **OPTIMER PHARMACEUTICALS' fidaxomicin**, an antibiotic to treat *C. difficile*, will be co-marketed by **Cubist Pharmaceuticals**.
- **Ovarian cancer** – Researchers reported at the American Association for Cancer Research (AACR) meeting that women with the BRCA2 mutation have an increased risk of ovarian cancer, but the same women also have a more favorable prognosis. The 5-year survival with the BRCA2 mutation was 61% vs. 46% for women with the BRCA1 mutation and 36% for women with neither mutation.
- **REGEN BIOLOGICS' Menaflex knee implant** – The FDA, as expected, revoked the knee implant's 510(k) clearance. The company said it is evaluating its options.
- **SUPERGEN** is acquiring **ASTEX THERAPEUTICS**, forming a company called **Astex Pharmaceuticals**.

NEWS IN BRIEF

ACTELION's Tracleer (bosentan) – another failed IPF trial

Tracleer missed the primary endpoint in the randomized, double-blind, placebo-controlled, 19.9 month BUILD-3 trial in mild-to-moderate idiopathic pulmonary fibrosis (IPF), showing no significant improvement vs. placebo in all-cause death or IPF worsening (≥10% decrease in forced vital capacity and ≥15% decrease in DLCO).

The results were published in the American Thoracic Society's ***American Journal of Respiratory and Critical Care Medicine***. Health-related quality of life scores also were not significantly different between bosentan and placebo.

Bariatric surgery – risk calculator developed

A study published in the ***Journal of the American College of Surgeons*** reported that a new risk calculator can help surgeons better select patients for bariatric surgery by predicting the risk of postoperative complications for individual patients. The calculator is available online at no charge. It allows surgeons to accurately model and predict patient postoperative morbidities, such as wound infections, sepsis, heart attack, kidney failure, lung failure, and other conditions.

Using data on 11,023 bariatric surgery patients, the researchers, led by Prateek Gupta, MD, of Creighton University Medical Center, validated the calculations. They determined that a recent MI, angina, stroke, high blood pressure, warfarin use, limited ability to perform basic activities of daily living, higher weight, and the type of bariatric procedure all were associated with increased risk.

BIOGEN IDEC/ELAN's Tysabri (natalizumab) – PML update

The Tysabri label was changed to include a table detailing the incidence of progressive multifocal leukoencephalopathy (PML) with this multiple sclerosis drug.

Tysabri and PML

Usage timeframe	Incidence of PML
<2 years	0.3 cases per 1,000 patients
2-3 years	1.5 cases per 1,000 patients
3-4 years	0.9 cases per 1,000 patients

Clusterin – fails as an Alzheimer's diagnostic

Serum levels of clusterin did not predict the risk of developing Alzheimer's disease in a prospective, population-based cohort study in the Netherlands, which was published in the ***Journal of the American Medical Association***. However, clusterin was markedly elevated in patients already diagnosed with the disease, and the levels significantly correlated with lower cognitive function scores. The findings suggest that clusterin has a reactive, not a causative, role in Alzheimer's.

COLUMBIA LABORATORIES/WATSON PHARMACEUTICALS' Prochieve (progesterone gel) – positive results

A study published in the journal ***Ultrasound in Obstetrics & Gynecology*** found that using this progesterone gel reduced the risk of early preterm delivery in women with a short cervix. The 458-patient study, done in collaboration with the National Institutes of Health, compared Prochieve to placebo starting in the second trimester. The rate of preterm delivery at <33 weeks was 8.9% with Prochieve vs. 16.1% with placebo. In addition, infants born to the Prochieve recipients had a lower rate of respiratory distress syndrome (3% vs. 7.6%). Prochieve, which is aimed at women who have already had one premature birth and are pregnant again, is not related to **KV Pharmaceutical**'s very expensive Makena (hydroxyprogesterone caproate injection), but it does compete with it.

Diabetes drugs – some are better than others

An observational Danish study, published in the ***European Heart Journal***, suggests that several commonly prescribed Type 2 diabetes drugs are not as effective at preventing death and cardiovascular diseases (e.g., stroke, MI) as metformin. The researchers studied 107,806 people over nearly 10 years and found that insulin secretagogues (sulfonylureas) – e.g., glimepiride, glyburide, glipizide, and tolbutamide – were associated with a greater risk of all-cause death, MI, stroke, or cardiovascular death than MI. Two other sulfonylureas (gliclazide and repaglinide) showed no significant efficacy difference vs. metformin.

The researchers cautioned that the findings may not mean the insulin secretagogues actually cause harm, just that they appear to be less effective than metformin. Tina Ken Schramm, MD, of Copenhagen University Hospital concluded, "Our study supports previous studies demonstrating that metformin may be less hazardous or more beneficial than most [insulin secretagogues]. This suggests that metformin should be the first drug of choice in Type 2 diabetes in most patients. The study shows there are important differences in the risk associated with different [insulin secretagogues], suggesting that gliclazide and maybe repaglinide are preferable, although in patients who have had a previous heart attack the most beneficial agents are metformin and gliclazide."

Imaging – Medicare likely to tighten rules

A Medicare Payment Advisory Commission (MedPAC) voted 15-1 to recommend that Medicare require clinicians who order more imaging studies than their peers to obtain prior authorization for advanced imaging. The panel also recommended that the Centers for Medicare and Medicaid Services (CMS) lower payments for successive imaging studies performed during the same imaging session.

If CMS follows the MedPAC recommendation, high-volume physicians would have to get preauthorization, while doctors with a low rate of use would only be subject to prior notification. A MedPAC analyst told the panel that 10% of physicians account for >50% of advanced imaging use, and a significant share of the 10% self-refer.

Preauthorization criteria are likely to be based on clinical guidelines developed by specialty groups, literature reviews, and expert panels.

MERCK

- Merck is buying **Inspire Pharmaceuticals**, which will expand Merck's portfolio of ophthalmic products, adding Azasite (azithromycin ophthalmic solution) for conjunctivitis and Elestat (epinastine) for allergic conjunctivitis. Earlier this year, Inspire reportedly gave up on denufosol for cystic fibrosis after it failed in a Phase III trial.
- **Gardasil** – The FDA turned down Merck's request to broaden the indication for this HPV vaccine to include women age 27-45. It is approved for females age 9-26.

NOVARTIS

- **Elidel (pimecrolimus)**, a skin cream to treat mild-to-moderate atopic dermatitis, is being sold to **Meda**.
- **Lumiracoxib (formerly Prexige, now Joicela)** – This arthritis pain medication was pulled from the market in 2007 due to reports of liver damage, but Novartis is hoping to get it back on the market and has resubmitted it to the European Medicines Agency, but only for patients who take an accompanying test that shows they aren't prone to liver damage. The company did not discuss plans for the drug in the U.S.

OPTIMER PHARMACEUTICALS' Dificid (fidaxomicin) – mixed FDA panel

The FDA's Anti-Infective Drugs Advisory Committee voted unanimously (13-0) that this first-in-class antibiotic, a macrocyclic RNA polymerase inhibitor to treat *Clostridium difficile* (*C. diff*), a potentially fatal bacterial infection of the colon, is safe and effective. However, the panel was split (6 to 6, with one abstention) on the drug's efficacy in preventing recurrences. Panel members also were concerned about GI bleeding and use in pregnant women, immunocompromised patients, and the elderly. This looks like the same problem **Salix** had with Xifaxan (rifaximin) in non-constipation IBS – lack of benefit on recurrences.

PFIZER

- **Tafamidis**, an oral treatment for transthyretin familial (TTR) amyloid polyneuropathy – which Pfizer got by buying **FoldRx Pharmaceuticals** in September 2010 – was rejected by the FDA, which sent the company a "refusal to file" letter saying the application was incomplete. Pfizer said it plans to resubmit the application as soon as possible and believes the additional information needed is available without conducting more clinical studies.
- Pfizer is **teaming up with Zacharon Pharmaceuticals**, which has technology for identifying drugs for lysosomal storage disorders, to develop drugs to treat rare diseases.

ROCHE

- **Trastuzumab emtansine (T-DM1) –** The company announced positive topline results in naïve HER2-positive metastatic breast cancer from the 137-patient, multicenter, two-arm, open-label, Phase II TDM-4450g trial. Progression-free survival (PFS) was significantly longer with T-DM1 vs. the combination of Herceptin (trastuzumab) and chemotherapy (docetaxel), and the T-DM1 patients had fewer adverse events.
- **GDC-0973 and GDC-0941 –** A Phase I study reported at AACR found that combining these two investigational cancer drugs – GDC-0973 is a MEK1/2 inhibitor and GDC-0941 is a PI3K inhibitor – did not produce any significant side effects.
- **GDC-0449 –** A small study presented at AACR found that this hedgehog pathway inhibitor quickly shrank basal cell carcinomas and prevented the formation of new lesions over three months of follow-up. However, the drug had significant toxicity, including loss of taste, weight loss, and muscle cramps, causing 20% of patients to discontinue treatment. This drug may be tolerable for very motivated patients but probably not for patients with sporadic or single lesions.

REGULATORY NEWS

New IT czar named

Farzad Mostashari, MD, was appointed as the new National Coordinator for Health Information Technology, replacing David Blumenthal, MD, who is returning to Harvard University. Previously, Dr. Mostashari was deputy national coordinator for programs and policy at ONC. Before that, he was assistant commissioner for a pimary-care information project at the New York City Health and Mental Hygiene Department.

Canadian device approval process changed

As of April 1, 2011, Health Canada said that once a drug or device filing is accepted, it would rule:

- in 120 days for medical devices.
- in 250 days for drugs.

Door opening to more off-label drug use in U.K.

In new draft guidance the U.K.'s General Medical Council said for the first time that general practitioners "should be allowed to give out a less costly alternative even if it is not licensed for that condition." The Council said doctors "must only check that the 'off-label' drug is safe and effective" and must tell their patients why they are prescribing it. The Council draft guidance says:

> *You should usually prescribe licensed medicines for their licensed uses; but you may prescribe off-label or unlicensed medicines outside an approved research protocol if there is no appropriately licensed alternative available or you are satisfied, on the basis of authoritative clinical guidance, that it is as safe and effective as an appropriately licensed alternative.*

Recent FDA approvals

- **ALPHATEC's Solus spinal device,** designed for use in anterior lumbar interbody fusion procedures, received FDA 510(k) clearance. The company plans an initial limited release, followed by a full launch later in the year.
- **ASTRAZENECA's Zactima (vandetanib) –** the first drug to gain FDA approval to treat metastatic medullary thyroid cancer. However, distribution will be restricted to a limited number of pharmacies due to the drug's serious side effects, which include an effect on the electrical activity of the heart, which could potentially cause irregular heartbeats and death. Richard Pazdur, MD, director of the FDA's Office of Oncology Drug Products in the Center for Drug Evaluation and Research (CDER), said the approval "underscores

FDA's commitment to approving treatments for patients with rare and difficult-to-treat diseases."

- **BOEHRINGER INGELHEIM's Viramune XR (nevirapine)** – approved for QD dosing in HIV.
- **CEPHEID's Cepheid Xpert C. difficile/Epi assay** received FDA 510(k) clearance for detection of the toxin B gene associated with *C. diff* infection.
- **COVIDIEN/EV3's Pipeline Embolization Device** – designed to block off aneurysms in the brain.
- **CUTERA's GenesisPlus laser** received FDA 510(k) clearance for treating fungal nail infections.
- **MERCK's Sylatron (subcutaneous peginterferon alfa-2b)** was approved to prevent melanoma recurrence following definitive surgical resection in patients with microscopic or gross nodal involvement.
- **ST. JUDE's Safire BLU and Therapy Cool Path** – two bi-directional radiofrequency ablation catheters for atrial fibrillation.
- **WATSON PHARMACEUTICAL's Nulecit,** a generic version of **Sanofi-Aventis**'s Ferrlecit (sodium ferric gluconate complex in sucrose injection), an injectable treatment for iron-deficiency anemia.
- **XENOPORT and GLAXOSMITHKLINE's Horizant ER (gabapentin enacarbil)** – a QD treatment for moderate-to-severe restless legs syndrome (RLS). It will carry the same warning about the risk of suicidality as gabapentin.

FDA monthly recall report

Each month the FDA issues a monthly report on its recalls, which sometimes contain items that were not announced earlier. These may have some interest for *Quick Takes* readers:

- **FDC LTD's ciprofloxacin ophthalmic solution** – ongoing recall initiated in February 2011 due to impurity concerns. This is an Indian pharma.
- **FRESENIUS's 2008T Hemodialysis Machine** – ongoing recall because the cursor on the dialysis screen may disappear and not respond to user input.
- **GE HEALTHCARE:**
  - **Senographe mammography systems** – ongoing recall initiated in July 2010 of 112 units after 3 units shipped to Japan were found to be missing the rating plate on the X-ray tube cover.
  - **MR systems** – recall of 9,142 units initiated by GE after it discovered a potential issue with gradient cables being inadvertently swapped during servicing.
  - **Signa MR diagnostic imaging devices** – 9 different devices (2,346 units in total) were recalled due to the potential for loss of patient monitoring and delayed alarms.
- **JOHNSON & JOHNSON/MCNEIL's Flexeril (cyclobenzaprine)** – 52,406 units, with ongoing recall initiated first in January 2011 and updated in March 2011 due to cGMP deviations, particularly cleaning issues.
- **MILLAR INSTRUMENTS' Mikro-Tip Angiographic Catheter** – The recall of this catheter, due to debris in the device, was upgraded to a Class I recall.
- **ROCHE's Acetaminophen Test System for use on the Roche/Hitachi** – company-initiated recall in December 2010 because the labeling does not have interference information for bilirubin, hemoglobin, or lipemia.
- **SANDOZ's triamterene and hydrochlorothiazide tablets** – ongoing recalled initiated in November 2010 due to cGMP deviations in the "compression process for the batch."
- **TEVA PHARMACEUTICALS USA's cabergoline** – ongoing recall initiated in December 2010 due to impurity concerns.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	April 2011	
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
April 27	**Merck's Victrelis** (boceprevir) for HCV	FDA's Antiviral Advisory Committee
April 27	**Medicis Aesthetics' Restylane** – expanded indication for augmentation of the lips	FDA's General and Plastic Surgery Devices Advisory Committee
April 28	**Vertex Pharmaceuticals' telaprevir** for HCV	FDA's Antiviral Advisory Committee
	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 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 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)
	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 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
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