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

- **ADHD drugs –** The FDA decided not to recommend changes in the use of stimulant ADHD drugs at this time, but the Agency plans to give a full update after it completes final analyses on the potential impact of the drugs on the risk of heart disease and strokes.

- **Advanced pancreatic neuroendocrine tumor (pNET) –** The FDA's Oncologic Drugs Advisory Committee voted unanimously to recommend approval of **Novartis**'s Afinitor (everolimus), but the panel said the label should clearly warn patients about potentially serious side effects. The panel also voted 8-2 in favor of approval for **Pfizer**'s Sutent (sunitinib), noting that the benefit was smaller and of shorter duration for Sutent, though it would like to see head-to-head studies conducted of Sutent vs. Afinitor or Sutent vs. streptozotocin.

- **ALCON** is now a division of **Novartis**. The merger of the two companies is complete, and Ciba Vision is under Alcon.

- **ALLERGAN's Lap-Band –** Two studies were published in ***Surgery for Obesity and Related Diseases*** on the safety and effectiveness of this obesity device. One study examined patients who received a Lap-Band after the failure of gastric bypass and found they achieved significant weight loss at two years post-banding. The second study found that Lap-Band procedures can be safely performed in a community medical practice, with patients experiencing meaningful excess weight loss.

- **CELGENE's Revlimid (lenalidomide) –** The FDA issued a warning to healthcare providers that this therapy for myelodysplastic syndrome and multiple myeloma may be associated with a higher risk of new cancers. The FDA did not restrict use but has a safety review under way.

- **CONFLUENCE PHARMACEUTICALS** licensed the rights to acamprosate for autism from Indiana University. Research by Dr. Craig Erickson, a pediatric psychiatrist at the Indiana University School of Medicine, found this alcohol-dependency drug may improve the language and social skills of patients with autism.

- **DAIICHI SANKYO's Benicar (olmesartan) –** The FDA decided, after a 10-month review, that the benefits of this angiotensin receptor blocker (ARB) outweigh its potential risks for the treatment of high blood pressure but is not recommended as a treatment to delay or prevent protein in the urine (microalbuminuria) in diabetic patients.

- **DELCATH SYSTEMS' Hepatic Chemosat Delivery System**, which can deliver chemotherapy to the liver, received a CE Mark. FDA review is ongoing.

- **FRESENIUS MEDICAL CARE's CombiSet** – The FDA sent the company a warning letter saying that some of the design changes made to this dialysis machine prior to the commercial launch were unapproved.

- **GLAXOSMITHKLINE's Alli (orlistat over-the-counter)**, a diet drug, is being sold, reportedly because it is no longer a "core" drug for the company. However, Sidney Wolfe, MD, director of Public Citizen's Health Research Group, filed a petition with the FDA asking the Agency to take both Alli and prescription Xenical off the market. Dr. Wolfe said new information obtained from FDA adverse event reports indicates orlistat was associated with 47 cases of acute pancreatitis and 73 cases of kidney stones.

- **JOHNSON & JOHNSON's weekly recall** – Two lots of 100-milligram tablets of Topamax (topiramate), a migraine drug, were recalled due to – *surprise* – a musty odor.

- **MERCK and INTERCELL's V-710** – A randomized, placebo-controlled Phase II/III trial of this vaccine for the prevention of *Staphylococcus aureus* infection in adult patients scheduled to undergo cardiothoracic surgery was halted pending further analyses of the risk:benefit profile. The action came at the recommendation of the Data Monitoring Committee after a pre-specified interim analysis of ~7,700 of the planned 8,044 patients, even though the trial did not meet futility criteria.

- **MOOG's Curlin ambulatory infusion pumps** were recalled due to a software anomaly that can result in a shutdown of the pump, potentially leading to serious injury and/or death. To date, there have been no adverse patient events reported to the company.

- **NOVARTIS's Tasigna (nilotinib)** – The company is discontinuing development of Tasigna as initial therapy for patients with gastrointestinal stromal tumors (GIST). The independent data monitoring committee recommended halting the trial because Tasigna patients were not doing significantly better than patients treated with Novartis's Gleevec (imatinib mesylate), which is the current standard therapy for GIST.

- **PENUMBRA's Penumbra Coil 400** – The FDA issued a Class I recall of this treatment for brain aneurysms, saying the pull wire on the delivery tool can slip out of place and allow premature detachment of the coil, potentially leading to migration that could cause serious injury including blood clots and stroke.

- **PFIZER and MEDIVATION's Dimebon (latrepirdine)** – The companies said the drug missed both co-primary endpoints in a 403-patient Phase III trial in Huntington's disease, but they are continuing to investigate it in mild-to-moderate Alzheimer's disease.

- **REGENERX BIOPHARMACEUTICALS' RGN-259** – The company reported positive preclinical results on this preservative-free ophthalmic drug for dry eye vs. three comparators: placebo, doxycycline, and **Allergan's** Restasis (cyclosporine A). Full data are expected at the Association for Research in Vision and Ophthalmology (ARVO) meeting in Ft. Lauderdale FL on May 3, 2011.

- **ROYAL PHILIPS ELECTRONICS' automated external defibrillators (AEDs)** – The FDA sent the company a warning letter saying it failed to adequately address problems linked to the AEDs and citing quality control problems at the company's Seattle plant.

- **SANOFI-AVENTIS** reportedly wants to sell its U.S. dermatology business, which includes the dermal filler Sculptra.

- **SERVIER's Vastarel (trimetazidine)** – French regulators (the Agence Française de Sécurité Sanitaire des Produits de Santé, or Afssaps) are recommending this treatment for vertigo, eye diseases, and tinnitus be taken off the market because it doesn't work and has side effects. Afssaps started the process for suspension, which includes a hearing and a referral to the European Medicines Agency (EMA).

NEWS IN BRIEF

BOEHRINGER INGELHEIM's Pradaxa (dabigatran) – FDA decision explained

When the FDA approved this anticoagulant for the reduction of the risk of stroke and systemic embolic in atrial fibrillation patients, many people were surprised that the Agency approved the high dose (150 mg) and not the low dose (110 mg) and approved a dose that hadn't been studied in clinical trials (75 mg).

The FDA apparently felt the need to publicly explain its decision. Three FDA officials – B. Nhi Beasley, PharmD; Ellis Unger, MD; and Robert Temple, MD – took the rather unusual, but not unprecedented, step of explaining the decision in some detail in an article this week in the ***New England Journal of Medicine***.

They said the decision "was based on our inability to identify any subgroup in which the use of the lower dose would not represent a substantial disadvantage…We were…unable to find any population for whom the availability of a lower dose [110 mg] would improve dabigatran's benefit:risk profile, and it appeared clear that most, if not all, patients should receive

the higher dose [150 mg]…For patients with severe renal impairment, in whom exposure increased by a factor of six, we reduced the dose to 75 mg…This decision was based not on efficacy and safety data but on pharmacokinetic and pharmacodynamic modeling."

Why not have two doses? The FDA officials explained, "Some patients who currently reject warfarin for fear of bleeding might have been willing to use dabigatran at the 100 mg dose, with its lower bleeding risk. Nevertheless, we concluded that to encourage the 'play it safe' option for patients and physicians represented an undesirable stimulus to use a less-effective regimen and would lead to unnecessary strokes and disability."

Among the key points they said influenced the approval decision were:

- Only 150 mg was superior to warfarin on efficacy.
- Only 110 mg was superior to warfarin in terms of bleeding.
- The risk of stroke/systemic embolism was reduced more with 150 mg. Users of the 110 mg dose would be more likely to have strokes, most likely embolic ones.
- Patients and doctors like choices, so two doses would have been nice "even at the cost of increased risk of stroke."
- Non-fatal and extracranial bleeding is "less clinically significant than strokes for most patients."
- In **elderly** patients, stroke was less with 150 mg but bleeding was higher. However, "most people would agree" that strokes are worse than non-fatal bleeding.
- In patients with **moderate renal impairment**, the stroke rate was lower with 150 mg and bleeding was no worse.

FDA Rationale for Approval of Pradaxa 150 mg (based on RE-LY trial findings)		
Measurement	**110 mg**	**150 mg**
Efficacy vs. warfarin	Non-inferior	Superior
Major bleeding vs. warfarin	Superior	Comparable
Risk of stroke/systemic embolism	--	Better
Risk of bleeding	Better	---
Safe and effective vs. warfarin	Yes but less compelling	Yes
Patients age ≥70		
Stroke and bleeding	Higher (1.9 per 100 Patient-years)	Lower (1.4 per 100 patient-years)
Major bleeding	4.4 per 100 PY	5.1 per 100 PY
Risk:benefit profile	---	Better
Patients with moderate renal impairment		
Stroke and bleeding	2.4 per 100 PY	1.3 per 100 PY
Major bleeding	5.7 per 100 PY	5.3 per 100 PY
Risk:benefit profile	---	Superior
Patients with a prior hemorrhage		
Additional major hemorrhage	16%	14%

- In patients with a **prior hemorrhage**, additional major hemorrhages were similar among all three groups, which means there is no benefit to transitioning patients to a lower dose if they have a bleeding episode.

CVS CAREMARK – should it be split?

Five consumer groups – Community Catalyst, Consumer Federation of America, Consumers Union, the National Legislative Association on Prescription Drug Prices, and U.S. PIRG – wrote to Federal Trade Commission Chair Jon Leibowitz urging that the CVS Caremark merger be dissolved. They claimed there is "strong evidence" that the merger has harmed consumers and accused the company of using confidential patient information from Caremark to steer consumers to CVS pharmacies.

Electronic health records (EHRs) – meaningful use readiness slipping

A quarterly survey by the College of Healthcare Information Management Executives (CHIME) conducted in March 2011 found that:

- 33% of CIOs expect their organizations to meet the meaningful use criteria and qualify for federal stimulus funding by September 30, 2011, the end of the first year of the program.
- Another 58% expect to qualify during Stage 1 but possibly not until late in federal fiscal years 2012 or 2013.
- There has been a steady decline in optimism about the ability to qualify for funding within the first six months of the federal program. Only 7.5% of respondents in November 2010 and 28% in August 2010 expected to qualify.
- A majority of CIOs said their organizations have yet to register for the federal program, which is the first step in declaring readiness to participate and subsequently demonstrating the meaningful use of EHRs.
  - 20% of CIOs at stand-alone hospitals have registered.
  - 30% of CIOs at multi-hospital systems have registered all their hospitals.
- 26% of CIOs from community hospitals expect to qualify for stimulus funding during the first year of the program. However, nearly two-thirds hope to qualify in late FY2012 or FY2013.
- 41% of CIOs are accelerating plans to implement EHRs, up from 36% in November 2010.
- Nearly 90% have concerns related to meeting meaningful use requirements.

- Nearly 75% are worried about legislative proposals to repeal incentive funding.

HIV drugs – California wants lower prices

California Treasurer Bill Lockyer wrote to eight pharmas asking them to extend special pricing for AIDS medications again this year because of the state's continued financial problems, and California Controller John Chiang sent a similar letter to **Gilead Sciences** requesting a reduction in the price of medications for California's AIDS Drug Assistance Program (ADAP).

Lockyer wrote, "California cannot afford to increase the budget for ADAP indefinitely in order to pay for higher drug prices. Nor can the state be put in the position of denying other essential health services in order to pay increasing drug costs. This tension must be resolved and in a manner that first serves Californians in need of healthcare."

Intracranial stents – medical management better

The National Institute of Neurological Diseases and Stroke halted the SAMMPRIS trial, a stroke prevention study, due to a higher rate of adverse events in the angioplasty/stenting arm than with medical therapy. With just 451 of the planned 764 patients enrolled, 14% of angioplasty patients (treated with **Boston Scientific**'s Gateway-Wingspan system) experienced a stroke or died within the first 30 days vs. 5.8% of patients treated with aggressive medical therapy alone, a highly significant difference.

The SAMMPRIS Executive Committee concluded that "the trial data currently available indicate that aggressive medical management alone is superior to angioplasty combined with stenting in patients with recent symptoms and high-grade intracranial arterial stenosis."

TEVA's delayed-release lansoprazole – taken off the market

The FDA warned risk healthcare providers and pharmacies that this orally disintegrating proton pump inhibitor tablet (used to treat ulcers, gastroesophageal reflux disease, etc.) can clog and block oral syringes and feeding tubes, including both gastric and jejunostomy tubes, when administered as a suspension through these devices. The FDA said the tablets might not fully disintegrate when water is added to them and/or they might disintegrate but later form clumps that can adhere to the inside walls of syringes and feeding tubes. Teva voluntarily withdrew the product from the market.

TNF inhibitors – cancer warning

The FDA said it continues to receive reports of a rare but aggressive cancer of white blood cells (hepatosplenic T-cell lymphoma, or HSTCL), primarily in adolescents and young adults being treated for Crohn's disease and ulcerative colitis – but also one psoriasis patient and two rheumatoid arthritis patients – with these drugs plus azathioprine or mercaptopurine. However, there also have been cases in patients on just azathioprine or mercaptopurine alone. The FDA is urging doctors to educate patients and caregivers on the signs and symptoms of HSTCL and to monitor for the emergence of malignancies in patients on any of these drugs.

REGULATORY NEWS

Congress urged to change FDA clinical trial requirements

In an article in FDLI's ***Food and Drug Policy Forum***, Steven Walker, co-founder of Abigail Alliance for Better Access to Developmental Drugs, urged Congress to revamp the clinical trials system, saying it is now outdated. Specifically, he recommended Congress:

- Give the FDA the statutory flexibility needed for establishing new approval standards.
- Annually review the state of the FDA's scientific performance.
- Create a new drug approval pathway.
- Improve investigational drug access mechanisms.

EMA view of Parkinson's disease drug trials

An article in ***Alzheimer Research Forum Newsletter*** reported on a talk at the International Conference on Alzheimer's and Parkinson's Diseases in March 2011 in Barcelona by Cristina Sampaio, MD, PhD, a Parkinson's disease (PD) expert from the University of Lisbon who serves on the Committee for Medicinal Products for Human Use (CHMP) of the EMA. Dr. Sampaio shared her perspective on clinical trials in Parkinson's disease. Among the points she made were:

- There are "plenty of effective treatments…The challenge… is to find a further drug that makes a difference…a disease-modifying (DM) drug that will change the course of the disease."
- The pipeline for PD is commonly said to be empty, "Few drugs are coming out, and the ones that do are not particularly novel. That is true in the sense that most drugs in the last phases of development are targeting symptomatic treatment, and most drugs that you can expect to see approved

in 2012 [and] 2013 are new formulations of well-known drugs."

- There are 181 compounds in development for PD, most of which are in early stages and not necessarily specific to PD.
- In the next few years, "we will see mostly symptomatic treatments."
- To obtain a claim in Europe for disease modification, a drug must interfere with the pathogenesis of the disease. This has been difficult to show until now, but genetic advances may make that possible in the future.
- The most important unmet medical need in this field is targeting the non-motor features of PD – depression, psychosis, and cognitive deficits. Historically, trials have had poor methodologic quality, and defining the populations has been difficult.
- Gene therapy is an active area and is showing "relatively good success" so far.
- There is a "serious hint" that there are clinical subtypes of PD, and these need to be identified and addressed specifically in trials.
- A way needs to be found to identify the pre-motor stage in PD.
- There is an "urgent " need for an immediate methodological improvement in trials targeting non-motor aspects of PD.

FDA handling of medical devices criticized

A Government Accountability Office (GAO) report concluded that the FDA is not measuring up in its handling of risky medical devices. The GAO said the FDA doesn't track recalled devices and doesn't follow up to be sure recalls are completed.

A GAO official told a congressional hearing, "Concerns persist about the effectiveness of the 510(k) process in general, including its ability to provide adequate assurance that devices are safe and effective…Gaps in FDA's postmarket surveillance show that unsafe and ineffective devices may continue to be used, despite being recalled." By federal law, all Class III medical devices must be approved through the premarket approval (PMA) process, but the GAO found that 228 Class III devices were cleared through the 510(k) process instead between 2003 and 2007. And the GAO found the problem persists, with 67 Class III devices cleared via 510(k) since 2009.

Federal budget – what it means for Medicare/Medicaid

President Obama's budget proposal would:

- Cut $480 billion from Medicare and Medicaid over the next 12 years.
- Give the Independent Payment Advisory Board (IPAB), which advised Congress on Medicare and Medicaid issues, more authority to recommend to Congress ways to cut the Medicare per-capita expenditure.
- Reform Medicaid by creating a single matching rate for all states.
- Limit "excessive" prescription drug payments "by leveraging Medicare's purchasing power."
- Speed up the availability of generic biologics.
- Prevent "pay for delay" agreements between brand and generic manufacturers.
- Implement "Medicaid management" of high prescribers and users of prescription drugs.
- Increase efforts against fraud and abuse in Medicare/Medicaid.
- Put ceilings on Medicaid payments for durable medical equipment.

U.K. doctors urged to start smaller on prescriptions

The U.K.'s ***Telegraph*** reported that health authorities are urging general practitioners to reduce the number of pills on a given prescription, which now costs £7.40, saying it is to reduce the cost to the National Health Service for wasted medicines. *Is the goal to stop waste or save money – or a little of both?*

Recent FDA approvals

- **COVIDIEN's DuraSeal Exact** spine surgery sealant will be launched in 2Q11.
- **DEVON MEDICAL PRODUCTS' ArterioFlow 7500** arterial pump for treating diabetic foot ulcers and other chronic lower-extremity conditions caused by poor blood circulation.
- **INTEGRA LIFESCIENCES** – three intervertebral body fusion devices. The company plans to launch them later this year.
- **NEUROVASX' cPAX Aneurysm Treatment System** was approved under a Humanitarian Device Exemption (HDE) for surgery on brain aneurysms that are difficult to manage because of their size (>10 mm) and shape, based on two studies with a total of 43 patients.

- **NEXERA MEDICAL's SpectraShield 9500**, a one-time-use surgical respirator that can protect health personnel from methicillin-resistant *Staphylococcus aureus* and two other bacteria, received 510(k) clearance.
- **NOVOCURE's NovoTTF** – The FDA approved this device that blasts glioblastoma multiforme (GBM) tumors with an electrical field despite a lukewarm advisory committee last month.
- **ST. JUDE MEDICAL's ShockGuard** system to prevent implantable cardioverter defibrillators (ICDs) from delivering inappropriate shocks was approved by both the FDA and European regulators.

FDA recall report

FDA regularly issues a report on its recalls, which sometimes contain items that were not announced individually. The following may have some interest for ***Quick Takes*** readers:

- **ABBOTT's CREON (pancrelipase)** – Company-initiated recall began in December 2010 because of stability issues.
- **ACTAVIS's Actavis Fentanyl Transdermal System 25 mcg/h strength** – A company-initiated recall began in October 2010 because of high dissolution results obtained during stability testing.
- **GLAXOSMITHKLINE's DynaCirc CR (isradipine controlled-release)** – Company-initiated recall due to dissolution issues.
- **JOHNSON & JOHNSON's Simponi (golimumab) SmartJect autoinjector pre-filled syringes** recalled because it can miscalibrate and not deliver the full dose.
- **MYLAN PHARMACEUTICALS' metformin** – Company-initiated recall began in February 2011 due to the possibility of oversized tablets.
- **SIEMENS:**
  - **Stratus troponin tests** for the diagnosis of acute myocardial infarction (AMI) – due to a low frequency of non-repeatable falsely elevated CTNI results without an associated error message.
  - **Acuson S2000 Ultrasound System** – because images captured from the device may be erroneous.
- **STRYKER BIOTECH's OP-1 Putty (OP-1, BMP-7, bone morphogenetic protein)** was recalled due to an unapproved change in the Preparation for Use section of the label, where 2.5 cc was replaced with 2-3 cc volume.
- **TEVA's topiramate** – Company-initiated recall began in February 2011 due to CGMP deviations.

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 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
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