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…

Trends-in-Medicine
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SHORT TAKES

- **AVEDRO's Keraflex KXL –** The FDA granted orphan drug status for this drug-device combination therapy for an eye condition, keratoconus.
- **BIONOR PHARMA ASA's Vacc-4x –** The company said a study showed ≤30% of Vacc-4x patients vs. 18% of placebo patients were able to stay off antiretroviral therapy >1 year after stopping it. The company plans three more trials, including one combining Vacc-4x and **Celgene's Revlimid** (lenalidomide).
- **EXALENZ BIOSCIENCE's BreathID –** The FDA granted a humanitarian device exemption (HDE) for this device to diagnose acute liver failure just a week after approving the design of a clinical trial to evaluate the device's efficacy and safety in detecting liver cancer at an early stage.
- **GENZYME's Cerezyme (imiglucerase) –** The company said it will delay shipments of this treatment for Gaucher disease, starting in October and continuing through January, due to supply problems stemming from process changes at the company's plant in Allston MA. Patients on twice-monthly dosing will be switched to once-monthly dosing during this period.
- **Healthcare IT –** The Office of the National Coordinator for Health Information Technology at the Department of Health and Human Services (HHS) released an 80-page final version of its Federal Health Information Technology Strategic Plan for 2011-2015. The plan will establish an HHS Inter-Division Task Force to establish policy direction on healthcare IT privacy and information exchange.
- **Lab tests –** Patients will have the right to obtain laboratory test results directly from labs under a proposed rule by HHS that amends patient provisions in two federal laws, CLIA (the Clinical Laboratory Improvement Amendments of 1988) and HIPAA.
- **MEDICIS PHARMACEUTICALS' LipoSonix –** Last week Medicis said it wanted to sell this ultrasound liposuction device business, and this week it found a buyer: **Solta Medical**.
- **PERKINELMER** is buying **Caliper Life Sciences**.
- **ROCHE/GENENTECH and CURIS' vismodegib**, an oral treatment for skin cancer, was submitted to the FDA.
- **RXI PHARMACEUTICALS' NeuVax –** The FDA lifted the clinical hold on this breast cancer vaccine for patients who cannot take **Roche/Genentech's Herceptin** (trastuzumab), which clears the way for a Phase III trial.

- **TOCRIS BIOSCIENCE's Fasudil**, a vasodilator approved to treat stroke patients, may have a role in treating some leukemias by blocking Rho-kinase (ROCK). In a study published in the journal ***Cancer Cell***, researchers from the Indiana University School of Medicine reported that Fasudil significantly prolonged the survival of mice with leukemia.
- **VIVUS' Qnexa (phentermine + topiramate)** – The FDA will allow Vivus to resubmit an application for this diet drug in October 2011 rather than making it wait for the December 2011 release of the results of a study of birth defects with topiramate. Vivus is seeking approval to treat obese people except women of childbearing potential.
- **WELLPOINT** will be using IBM's Watson computer, starting in 2012, to analyze patient records and medical information to identify possible treatments, starting with oncology but eventually for other applications, including patient access. The IBM application will compare a patient's symptoms and history to information in textbooks and medical journals, and, in just a few seconds, present several possible diagnoses or treatments.

NEWS IN BRIEF

AETERNA ZENTARIS' AEZS-108 – positive Phase II results in endometrial cancer

Positive Phase II efficacy results in advanced endometrial cancer with this cytotoxic luteinizing hormone-releasing hormone (LHRH) analog were reported at the European Society of Gynaecological Oncology (ESGO) meeting in Milan, Italy.

Response rate (by RECIST), the primary endpoint, was 30.8% with AEZS-108, and the clinical benefit rate (CR+PR+SD) was 74.4%. Overall survival with AEZS-108 monotherapy was similar to triple combination chemotherapy, but with lower toxicity.

A pivotal trial for FDA and European registration is being planned.

Alzheimer's disease – take B vitamins and folic acid?

In a 270-patient study reported at the British Science Festival and published in the ***International Journal of Geriatric Psychiatry***, researchers reported high doses of vitamin B12 (0.5 mg), vitamin B6 (20 mg), and folic acid (0.8 mg) reduced memory decline by 70% in elderly patients with mild cognitive impairment (MCI). The vitamins also reduced the rate of brain shrinkage at 2 years by 50%. A 1,000-patient trial is now planned in the U.K.

AMGEN's Xgeva (denosumab) – not cost-effective

A study by Analysis Group (a consulting firm) found that Xgeva may not be cost-effective for the prevention of skeletal-related events (SRE) in breast cancer with bone metastasis, researchers cautioned. The researchers estimated that:

- The number needed to treat (NNT) to prevent one SRE was 17.3.
- This came at a cost of $270,000.
- SREs were 30.7% with denosumab vs. 36.5% with **Novartis' Zometa** (zoledronic acid), a bisphosphonate.
- First on-treatment pathologic fracture was an absolute 2.7% lower with denosumab (20.7% vs. 23.3%), for an NNT of 37.4.
- The yearly cost of Xgeva is $16,830 and $8,631 for Zometa.
- The cost of preventing one SRE was $142,127 with Xgeva, and the cost of preventing one pathological fracture would be $307,016.

BOEHRINGER INGELHEIM's Pradaxa (dabigatran) – more safety concerns

Pradaxa has been blamed for two deaths in New Zealand and dozens of severe bleeding cases, some of which required multiple blood transfusions or surgical intervention. The anticoagulant was added to the country's formulary three months ago, but now New Zealand regulators are being criticized for approving it too quickly. U.S. and European doctors have been complaining of excessive GI bleeding, but the New Zealand cases were mostly in elderly (>age 75) patients who coughed up blood and had rectal and intracranial bleeding.

GLAXOSMITHKLINE's Zofran (ondansetron) and generics – heart rhythm warning

The FDA warned doctors and patients that this anti-nausea drug (a 5-HT3 receptor agonist) may increase the risk of the QT prolongation and even lead to abnormal and potentially fatal heart rhythm, including Torsade de Pointes. GSK has been ordered to conduct a thorough QT study to determine the degree to which Zofran causes QT prolongation, and the labels are being revised to include a warning to avoid use in patients with congenital long QT syndrome and to use EKGs to monitor patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, brady-arrhythmias, or who are taking other medications that can lead to QT prolongation.

INNORA's IN.PACT Pacific – positive results

This paclitaxel-coated balloon catheter showed better efficacy at 6 months than an uncoated balloon for the treatment of peripheral artery disease in the randomized PACIFIER trial, conducted in Germany. The results of the trial, which were presented at the Cardiovascular and Interventional Radiological Society of Europe meeting in Munich, showed: -0.05 mm late loss with IN.PACT vs. 0.61 mm with a bare balloon (p=0.003). A composite of death, amputation, and target lesion revascularization (TLR) also significantly favored the paclitaxel-coated balloon (7.3% vs. 26.8%, p=0.02).

INTUITIVE SURGICAL'S DA VINCI – value of robotics for endometrial cancer challenged

A study presented at the European Society of Gynecological Oncology found that robotics (translation: da Vinci, even though it wasn't specifically mentioned) increased the cost of a hysterectomy without improving the outcome vs. conventional laparoscopic procedures for endometrial cancer. Furthermore, a robotic procedure cost ~$1,600 more.

A database analysis identified 2,464 hysterectomy patients, with 41.7% having a laparoscopic hysterectomy and 58.3% having a robotic procedure. A multivariate analysis found that robotic procedures were more common at large hospitals and non-teaching hospitals, but less common among blacks, the uninsured, and rural patients.

Perioperative morbidity was not significantly different (9.8% with laparoscopic hysterectomy vs. 8.1% robotically, p=0.018). There was no difference in the frequency of intra-operative injury, transfusion, prolonged hospitalization, or non-routine discharge.

The question is whether the robotic trend will slow down.

MENARINI's abagovomab – failed in ovarian cancer

In data presented at the European Society of Gynecological Oncology meeting, this monoclonal antibody against CA125 did not slow progression of advanced ovarian cancer at all. In a large randomized trial vs. placebo post platinum-taxane chemotherapy, PFS was identical at 13.2 months. Furthermore, a subgroup analysis failed to identify any patients who benefited from the treatment.

PFIZER

- **Pristiq (desvenlafaxine).** The FDA rejected a new indication for prevention of hot flashes and other menopausal vasomotor symptoms, sending Pfizer a complete response letter. Pristiq is already approved to treat major depressive disorder.
- **Xanax (alprazolam).** A Kentucky clinic stopped writing new prescriptions for Xanax and generic alprazolam in April and plans to wean patients off the anti-anxiety medication completely by the end of 2011.

TEVA PHARMACEUTICAL INDUSTRIES

- Was notified by the FDA it has resolved the manufacturing issues raised by the FDA at its Jerusalem plant.
- Is investing in **Cocrystal Discovery**, with the goal of developing once-daily antiviral therapies, such as a drug for hepatitis C.
- Is buying a larger stake in **CureTech** after positive Phase II results were announced for CT-011 in lymphoma.

TRANSCEPT PHARMACEUTICALS' Intermezzo (zolpidem tartrate) – being resubmitted to FDA

In July 2011 the FDA rejected this insomnia drug, citing safety concerns. The company said it plans to resubmit the drug to the FDA this month, does not expect additional safety trials will be required, and hopes for an FDA decision in ~2 months. The company has proposed that the recommended dose be cut in half for women (to 1.75 mg), that patients take the drug only if they have ≥4 hours of sleep remaining, and that patients not drive within five hours of taking it or within an hour of waking.

VAXGEN's RV144 – works but only in Thais

In data presented at the annual AIDS Vaccine Conference, researchers reported that at the end of a 3.5-year trial, this AIDS vaccine prevented infection in ~30% of the 16,000 Thai volunteers who received it. However, the researchers warned the vaccine and the immune response it created were specific to the type of HIV in Thailand and the vaccine formulation used there.

REGULATORY NEWS

FDA jurisdiction over compounding weakened

In 2010, the FDA challenged **Franck's Pharmacy** in Florida, a compounding lab – and by extension all veterinary compounding pharmacies – charging that they violated the Animal Medicinal Use Clarification Act and other regulations. However, a U.S. District Court judge ruled against the FDA, saying the Agency does not have jurisdiction over compounding by pharmacies that do not engage in manufacturing.

FDA reorganizes CDER's oncology office

The Center for Drug Evaluation and Research's (CDER's) Office of Oncology Drug Products has been reorganized and renamed the Office of Hematology and Oncology Products (OHOP). Richard Pazdur, MD, will continue to be the director of the office, and he will continue to head the agency-wide oncology program that coordinates oncology activities within the FDA as well as with external stakeholders. That program will remain in OHOP.

CDER director Janet Woodcock, MD, said she doesn't expect the reorganization to slow down pending applications, adding, "In fact, we expect to see greater efficiencies that will better support our work to get cancer treatments to patients."

Previously there were three divisions: Division of Hematology Products (DHP), Division of Drug Oncology Products (DDOP), and Division of Biologic Oncology Products (DBOP). Now there are four:

- Division of Hematology Products (DHP), which will review hematology therapies.
- Division of Oncology Products 1 (DOP1), which will review breast, gynecologic, genitorurinary, and non-hematologist supportive care.
- Division of Oncology Products 2 (DOP2), which will review GI, lung and head & neck, neuro-oncology and rare cancers, pediatric solid tumors, melanoma, and sarcoma.
- Division of Hematology Oncology Toxicology (DHOT). This new division will review non-clinical pharmacology and toxicology aspects of cancer therapies.

Public doesn't understand FDA approval process

An Internet survey of 2,944 people by Knowledge Networks, published in the ***Archives of Internal Medicine***, found:

- Many consumers mistakenly believe new prescription drugs are always safer than those with long track records.
- 40% wrongly believe the FDA approves only "extremely effective" drugs.
- 25% mistakenly believe the FDA allows approval of drugs without serious side effects.

Medicare payments to physicians to hit specialists

The good news at a two-day meeting of the Medicare Payment Advisory Commission (MedPAC) was that the MedPAC staff agreed the Sustainable Growth Rate that is used to calculate physician payments under Medicare be revised. The bad news was that they proposed a plan under which specialists would be the hardest hit.

The proposal calls for cuts, but only among specialty providers, who would see a 5.9% reduction per year for three years and then a freeze on reimbursement for the next seven years. Reimbursement rates for primary care physicians would not be cut, but they would be frozen at current levels for the next 10 years.

Not surprisingly, specialty physicians and their associations are not happy.

The MedPAC staff also recommended a change in the way relative value units (RVUs) are figured out, suggesting that electronic health records and billing/scheduling information be used instead of physician surveys.

The current fee-for-service payment system also was criticized, and the staff recommended that the Centers for Medicare and Medicaid (CMS) encourage providers to join accountable care organizations or other practice models that incorporate bundled payments or capitation systems.

HHS launches Million Hearts program

HHS, along with several partners, including the American Heart Association, launched Million Hearts, an initiative that aims to prevent 1 million heart attacks and strokes over the next five years. The program has two goals: encouraging Americans to make healthier choices – e.g., stopping smoking and cutting sodium and fat – and improving care, with a focus on ABCS (aspirin, blood pressure control, cholesterol management, and, again, smoking cessation).

By empowering Americans to make healthy choices and improving care, Million Hearts strives to achieve the following specific goals:

ABCS Goals		
Item	**Baseline**	**2017 goal**
Aspirin use for people at high risk	47%	65%
Blood pressure control	46%	65%
Effective treatment of high LDL	33%	65%
Smoking prevalence	19%	17%
Sodium intake (average)	3.5 g/day	20% reduction
Artificial transfat consumption (average)	1% of calories/day	50% reduction

European regulatory actions

- **NAVISCAN's high-resolution PET scanner and PET-guided biopsy accessory** got a CE Mark for tomographic imaging of breast tumors.

- **OPTIMEDICA's Catalys**, a laser system with a femto-second laser and OCT for use in cataract surgery, received a CE Mark.
- **SANTEN PHARMACEUTICAL's sirolimus (DE-109)** received orphan drug status as a treatment for chronic non-infectious uveitis. DE-109 is currently in Phase III development.

FDA recalls

- **MEDTRONIC's SynchroMed II Implantable Infusion Pump (Model 8637) –** the recall was upgraded to a Class I recall due to the potential for reduced battery performance. A Medtronic analysis found the problem comes from formation of a film within the pump battery.
- **QUALITEST PHARMACEUTICALS – all of the company's oral contraceptives –** a nationwide, retail-level recall due to a packaging error that may result in the daily regimen for these products being incorrect and potentially leaving women without adequate contraception.

FDA warning letters

DAIICHI SANKYO/LUITPOLD PHARMACEUTICALS – for "significant" and repeated violations of good-manufacturing rules at its injectable drugs plant in Shirley NY.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	September 2011	
September 20	**Overview of the research program** in the Laboratory of Enteric and Sexually Transmitted Diseases, Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and Review, CBER, FDA	FDA's Vaccines and Related Biological Products Advisory Committee meeting at NIH ***via teleconference***
September 26	**Drug shortages**	FDA public workshop
September 26-27	**Tissue adhesive materials**	FDA workshop on facilitating innovation in these products
September 30	Institute of Medicine's recommendations for FDA's reform of the **510(k) device clearance program**	Public comment deadline
	October 2011	
October 12	**FDA guidance on diagnostic tests** being developed simultaneously with a drug/biologic	New deadline for industry comment
October 13	**Cook's Zilver-PTX** paclitaxel-eluting, non-polymer stent	FDA's Circulatory System Devices Advisory Committee
October 13	**Highly multiplexed microbiology/medical countermeasure (MCM) devices,** for identifying potential disease etiology	FDA public meeting
October 14	**GenProbe's Progensa PCA3 assay** to aid in the decision for repeat biopsyin men age ≥50 with ≥1 previous negative prostate biopsy	FDA's Immunology Devices Advisory Committee - postponed
October 17	**Teva Neuroscience's Azilect** (rasagiline mesylate) for a new indication in Parkinson's disease	FDA's Peripheral and Central Nervous System Drugs Advisory Committee
October 28	**Bristol-Myers Squibb** and **AstraZeneca's dapagliflozin,** the first SGLT-2 for Type 2 diabetes	PDUFA date
October 28	**Pacira Pharmaceuticals' Exparel** (bupivacaine ER), a painkiller	PDUFA date
	Other 2011 meetings/events	
2H11	**Abbott's RX Acculink** carotid stent	FDA final decision expected
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
November 2	**Merck's Vytorin** (ezetimibe/simvastatin) and **Zetia** (ezetimibe), supplemental NDA to reduce major cardiovascular events in patients with chronic kidney disease (CKD), based on the results of the SHARP trial	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
November 5	**Johnson & Johnson's Xarelto** (rivaroxaban) for stroke prevention in AFib	PDUFA date
November 16	**Pneumococcal 13v vaccine** safety and immunogencity in adults >age 50	FDA's Vaccines and Related Biological Products Advisory Committee
November 18	**Regeneron's Eylea** (aflibercept, VEGF Trap-Eye) for wet AMD	New PDUFA date
December	**Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to be completed	Company announcement or medical conference presentation
December 8	**Antares Pharma's Anturol** (transdermal oxybutynin ATD gel), for overactive bladder	PDUFA date
December 13	**Endo Pharmaceuticals' Opana** (extended-release oxymorphone), a painkiller	PDUFA date
	2012	
January	**Pfizer's Prevnar 13** (PCV13), a pneumococcal vaccine for adults	PDUFA date
January 28	**Eli Lilly, Amylin Pharmaceuticals and Alkermes' Bydureon** (weekly exenatide XR), an injectable drug for Type 2 diabetes	FDA decision date
February	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation
February 17	**Corcept Therapeutics' Corlux** (mifepristone) for Cushing's syndrome	PDUFA date
February 28	**Pfizer's axitinib** for advanced renal cell carcinoma	PDUFA date (*approximate*)
March 27	**Affymax and Takeda's peginesatide** for anemia	PDUFA date
April 26	**Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in prostate cancer	PDUFA date
April 27	**Salix Pharmaceuticals and Progenics Pharmaceuticals' Relistor** (methylnaltrexone injection) for opioid-induced constipation	PDUFA date
April 29	**Vivus' avanafil** for erectile dysfunction	PDUFA date
April 30	**Baxter and Halozyme's HyQ** for immunodeficiency	PDUFA date