TRENDS-in-MEDICINE

October 10, 2010

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Quick Takes

…Highlights from this week's news affecting drugs and devices in development…

SHORT TAKES

- **Alzheimer's disease –** The U.K.'s National Institute for Health and Clinical Excellence (NICE) issued draft guidance that would reverse a 2006 decision that restricts patient access to three drugs for mild-to-moderate Alzheimer's – Eisai/Pfizer's Aricept (donepezil), Novartis's Exelon (rivastigmine), and Shire's Reminyl (galantamne).

- **ANGIODYNAMICS' NanoKnife –** At least 13 U.S. hospitals are using – and promoting – this device as a treatment for cancer, but some physicians are questioning its use because it was approved via the FDA's 510(k) approval process, with tests on only animals and a small number of humans.

- **AXOLOTL's Elysium Exchange** was chosen by the Health Information Partnership for Tennessee to be the platform for its health information exchange (HIE).

- **BRISTOL-MYERS SQUIBB's Orencia (abatacept)** failed to prevent flares in patients with systemic lupus erythematosus (SLE), according to a study published in ***Arthritis & Rheumatism***. In the Phase II study of 180 patients with active lupus, new flares developed in 79.7% of Orencia patients vs. 82.5% with placebo, a treatment difference of only 3.5%, and there were more adverse events with Orencia (19.8% vs. 6.8%).

- **CAREMARK –** A group of Texas pharmacies filed a lawsuit against CVS Caremark, saying it violated racketeering and privacy laws. The lawsuit accuses CVS Caremark of gaining too much control over patient information, including files from independent pharmacies, and using that information for direct marketing to patients and doctors.

- **GENESCIENCE PHARMACEUTICALS**, a Chinese company, and its founder/CEO Dr. Lei Jin pled guilty to illegally distributing Jintropin, a human growth hormone, in the U.S.

- **HIV drugs –** According to a ***Dallas Morning News*** report, the Texas HIV Medication Program, which supplies anti-retroviral drugs to HIV and AIDS patients who can't afford them, will run out of money in the next two years and be forced to cut off enrollment, tighten eligibility, or stop covering some drugs unless the state provides an additional $23 million. Enrollment reportedly has reached record levels due to the recession and job losses.

- **INTERMUNE's (danoprevir, RG7227/ITMN-191) –** Roche bought full worldwide development and commercialization rights to (sole ownership of) danoprevir, a second generation NS3/4A protease inhibitor for hepatitis C that is currently in Phase II development. Roche said the deal "increases our ability to rapidly develop combinations of our own hepatitis C compounds with molecules from other companies."

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- **JOHNSON & JOHNSON** completed negotiations to buy Dutch vaccine manufacturer, **Crucell**, giving J&J a vaccine platform.

- **JOHNSON & JOHNSON's Nucynta (tapentadol ER)** – J&J received a complete-response letter from the FDA, which wants additional information about the drug's conversion to a break- and crush-resistant formulation.

- **NEOPROBE's Lymphoseek** – The FDA wants more safety data for this imaging agent, so the company is delaying filing the NDA until 1Q11.

- **NOVARTIS** plans to use technology from **Synthetic Genomics Vaccines** to try to cut the time it takes to develop flu shots by two months. The companies will work together to create seed viruses.

- **NOVARTIS's Gilenya (fingolimod)** – Novartis said it will pay out-of-pocket costs (as much as $800 monthly in copays) for ***non***-Medicare patients who take this oral multiple sclerosis (MS) therapy, which is priced at ~$4,000 a month. Novartis's offer is not based on a patient's income or medical status.

- **NOVARTIS's Mycograb (efungumab)** – Development of this drug to treat a common yeast infection has been halted.

- **NOVARTIS's secukinumab** – Phase I and Phase IIa data indicated this anti-IL-17A cytokine has efficacy in rheumatoid arthritis, uveitis, and psoriasis and could possibly be an alternative to TNF-inhibitors.

- **NOVARTIS/HUMAN GENOME SCIENCES' Zalbin/Joulferon (albinterferon alfa-2b)** – Development was ended for this potential hepatitis C drug after new data from a Phase II study showed that it is only as effective as currently approved therapies and requires more injections. The companies' discussions with European and U.S. regulators suggested that regulatory approval was doubt-ful.

- **ONYX's carfilzomib** – FDA approval has been delayed for manufacturing reasons.

- **Opioids** – The Drug Enforcement Administration (DEA) is investigating pharmacists in about five states for dispensing narcotics to nursing homes without direct written orders from a doctor.

- **Pharma investigation** – The U.S. Justice Department and the Securities and Exchange Commission (SEC) are looking into allegations that major pharmas – Merck, AstraZeneca, Bristol-Myers Squibb, and GlaxoSmithKline – might be bribing officials overseas to boost drug sales and to speed regulatory approvals.

- **PFIZER** may sell its **Capsugel** unit, which makes capsules for drugs and dietary supplements, after a review that will be completed in 1Q11. Pfizer is looking to offset some of the revenue it will start losing next year when the company faces competition from cheaper generic copies of Lipitor. Pfizer hired Morgan Stanley to conduct a strategic review of the unit, a process that will be completed by the end of 1Q11.

- **PFIZER's Lipitor (atorvastatin)** – Pfizer voluntarily recalled 191,000 bottles of Lipitor in the U.S. and Canada in August 2010 because of reports of an "uncharacteristic" odor (a musty smell) related to the bottles in which the drug was packaged. The recall included seven lots of Lipitor plus three lots of generic atorvastatin that were supplied to a Canadian firm.

- **PFIZER's tasocitinib (CP-690,550)** met the primary endpoint in a Phase II study of 197 psoriasis patients, reducing symptoms ≥75% after 12 weeks. The data were presented in posters at the European Academy of Dermatology and Venereology in Gothenburg, Sweden.

- **Radiology** – In a study reported in the ***Journal of the American Medical Association***, researchers from Johns Hopkins found that the use of advanced radiology tests to assess injuries increased ~3-fold in U.S. emergency departments (EDs) over the last 10 years. Several reasons have been suggested for the increase, including: increased patient demand, doctors hoping for more diagnostic information, better ED access to scanners, and doctors' fears of lawsuits for failing to order the tests.

- **SALIX PHARMACEUTICALS' Xifaxan (rifaximin)** – The FDA extended until March 7, 2011, a review of Xifaxan to treat patients with non-constipation irritable bowel syndrome. The drug is already approved for travelers' diarrhea and hepatic encephalopathy caused by advanced liver disease.

- **Selenium** – The FDA was ordered by a federal court in Washington DC to shorten three health claims for selenium supplements. The court ruled the lengthy descriptions of mixed study results on the disease-fighting benefits of selenium were unconstitutional and should be revised.

- **TARGACEPT/ASTRAZENECA's AZD-1446** failed to improve symptoms in a Phase II study vs. placebo in attention deficit/hyperactivity disorder (ADHD), and the companies are expected to abandon development.

- **Transcatheter aortic valve implantation (TAVI) –** A ***CRTonline.org*** poll asked whether cardiologists believe it is ethical to randomize patients with aortic stenosis to balloon valvuloplasty or medical therapy alone given the results of the PARTNER trial of Edwards Lifesciences Sapien valve, and 71% said no.
- **VARIAN MEDICAL SYSTEMS** and **IMRIS** are co-developing a new MR-guided radiation therapy system that combines IMRIS's MR imaging technology with Varian's recently introduced TrueBeam system to enable the use of MRI during radiotherapy treatments for cancer.

NEWS IN BRIEF

ACTELION's Tracleer (bosentan) and Ventavis (inhaled iloprost) – FDA warning letter

The FDA sent a warning letter to Actelion's U.S. subsidiary for failing to report ~3,500 patient deaths in connection with Tracleer and Ventavis, which are approved to treat pulmonary arterial hypertension (PAH). The FDA said the company did not have an adequate basis for not reporting them.

ABBOTT LABORATORIES' Meridia (sibutramine) – withdrawn from U.S. market

At the request of the FDA, Abbott is voluntarily withdrawing Meridia from the U.S. market because of data from the European SCOUT trial which indicated an increased risk of heart attack and stroke. In making the announcement, Dr. John Jenkins, director of the FDA's Office of New Drugs, Center for Drug Evaluation and Research (CDER), said, "Meridia's continued availability is not justified when you compare the very modest weight loss that people achieve on this drug to their risk of heart attack or stroke. Physicians are advised to stop prescribing Meridia to their patients, and patients should stop taking this medication."

Dr. Gerald Dal Pan, director of the FDA's Office of Surveillance and Epidemiology, CDER, added, "The patients in the European SCOUT trial did not have the same characteristics as the patients for the approved indication in the U.S.; however, these results, combined with other available safety data raised serious questions about Meridia's safety for all patient groups."

ALLERGAN's Botox (onabotulinumtoxinA) – federal investigation settled

The 2.5 year federal investigation into allegedly misleading marketing of Botox is over. A judge in Georgia approved Allergan's decision to pay $600 million and plead guilty to misbranding the product. The "sentencing" came a month after the company said it would admit to a charge that the company's marketing tactics led physicians to use Botox for unapproved uses such as headaches, pain, and cerebral palsy in children between 2000 to 2005. Allergan also agreed to a five-year corporate integrity agreement (CIA), requiring it to disclose on its website payments to doctors and to provide annual certification by senior executives and board members that divisions meet federal healthcare requirements. Remember that a CIA is not a walk in the park, and companies (e.g., Tenet Healthcare) have gotten into trouble with the government even while under a CIA.

AMGEN's AMG-386 – better results with updated data

Updated results from a Phase II trial were presented at the European Society for Medical Oncology (ESMO) meeting in Milan, Italy. They showed that adding AMG-386, an anti-angiogenesis drug, to chemotherapy extended progression-free survival (PFS) by several weeks in advanced ovarian cancer – 7.3 months at the high dose, 7.4 months at the low dose, and 5 months with chemotherapy (paclitaxel) alone. In the 161-patient study, overall survival for patients on the high dose was 22.5 months vs. 20.4 months for patients on the lower dose, and 20.9 months for patients on chemotherapy alone. A Phase III trial of AMG-386 + paclitaxel is underway in ovarian, primary peritoneal, and fallopian tube cancers.

ASTRAZENECA's Brilinta (ticagrelor) – CV trial planned

The PEGASUS-TIMI-54 trial to assess the safety and long-term efficacy of Brilinta to reduce cardiovascular (CV) events vs. aspirin in acute coronary syndrome (ACS) patients is being initiated by the company and the TIMI Study Group. The trial will enroll 21,000 patients in >30 countries, randomized to placebo or Brilinta 60 mg or 90 mg BID for at least 12 months. All patients will also take 75-150 mg aspirin daily. The primary endpoint will be time-to-first-occurrence of any CV event (CV death, non-fatal MI, or non-fatal stroke). Patient enrollment is expected to start in 4Q10.

CELLDEX THERAPEUTICS CDX-110 – possible immunotherapy vaccine for brain cancer

The Celldex vaccine is the first to zero in on proteins only present in cancer cells, which could reduce the number of side effects often experienced by patients given other vaccines. The hope is that the vaccine could help as many as a third of the 10,000 new cases in the U.S. annually of an aggressive type of brain cancer with a current average survival of ~14 months,

with a particular gene mutation that fuels the aggressive growth. The vaccine reportedly "educates" the immune system to produce antibodies that attack the tumor very specifically.

Cystic fibrosis
– *some* benefits to recombinant human growth hormone

A meta-analysis by University of Connecticut researchers of eight observational studies and 10 clinical trials found "some evidence" that giving recombinant human growth hormone to CF patients may improve bone mineral content, reduce the need for in-patient care, have a beneficial effect on weight, height, and pulmonary measures. However, the study, which was funded by the U.S. Department of Health and Human Services and reported in ***Pediatrics***, found no evidence that the therapy prolongs life or improves health-related quality of life.

Depression
– FDA struggling with requirements for depression devices

The FDA's Neurological Devices Advisory Committee told the FDA that investigators have to do more than simply ask patients if they failed to respond to medication before entering a trial for a device to treat depression. Instead, they recommended a lead-in period, with only patients who failed to respond to medication during that lead-in would receive a device. The panel didn't agree on how many patients would be needed in a pivotal trial, how many drugs patients should have to fail before being considered for device therapy, or how many suicides would be acceptable in a depression device trial. The FDA is not actually preparing guidelines for depression devices, but the hope was that the panel would help clarify what the FDA wants to see with these devices.

Electronic medical records (EMRs)
– still need tweaking

A University of Pennsylvania study reported in the ***Philadelphia Inquirer*** suggests that computerized physician order entry (CPOE) still needs refining. The researchers compared two groups of doctors on their use of two drugs with potentially dangerous interactions: the blood thinner warfarin and the antibiotic trimethoprim-sulfamethoxazole.

To test if a hard-to-override alert would reduce the drugs' use together, the researchers had the system stop those orders for half the users while leaving the old system in place for the others. The computerized "stops" had the desired effect, with fewer prescriptions of both drugs together made by the first group. The study was stopped early because of four cases in which patients had long delays in getting the needed drugs.

EVOTEC and SHIONOGI – drug discovery alliance

Evotec has entered into a multiple target drug discovery collaboration with Shionogi to identify small molecule modulators of various protein-protein interaction targets. Evotec will apply its proprietary and integrated fragment-based drug discovery platform, EVOlution, to the program. The key benefit of this platform for the selection of target-specific strategies is its versatility, combining biochemical and biophysical techniques including nuclear magnetic resonance (NMR), surface plasmon resonance (SPR), and x-ray crystallography. Within this collaboration, EVOlution will be used to investigate protein-protein interactions on targets selected by Shionogi.

FRESENIUS MEDICAL – gets FDA warning

Fresenius received a 483 letter from the FDA for failing to adequately investigate and repair issues with two kidney-dialysis products – Optiflux Dialyzers and Liberty Cycler Sets. The FDA said Fresenius did not establish and maintain adequate procedures for implementing corrective and preventive actions. Fresenius responded to the letter, but the FDA decided that the response was "inadequate." The FDA also expressed concern with Fresenius's oversight of its contract manufacturers, particularly ones producing drugs such as PhosLo (calcium acetate).

Healthcare reform
– judge upholds mandate that people buy insurance

A federal judge in Michigan ruled that Congress ***does*** have the power to require individuals to purchase health insurance. Opponents of the law have claimed it is unconstitutional, but the judge disagreed, saying the challenge to the law "failed on the merits." The judge also rejected the argument that the penalty to be assessed on people who don't purchase health insurance is an unconstitutional tax.

INFINITY PHARMACEUTICALS' IPI-926
– positive early results

Preliminary results from an open-label, dose-escalation, Phase I study in advanced/metastatic solid tumors showed this oral small molecule Hedgehog pathway inhibitor was well tolerated and resulted in clinical activity in patients with basal cell carcinoma (BCC). The most common adverse events were

Grade 1 and 2 fatigue and nausea, with Grade 3 transaminitis occurring in four patients, but no Grade 4 or 5 adverse events.

A Phase Ib/II study in combination with Lilly's Gemzar (gemcitabine) in patients with previously untreated, metastatic pancreatic cancer currently is enrolling patients.

PFIZER's Arimidex (anastrozole) – benefits continue long term

Ten-year data from a large trial presented at the American Society of Clinical Oncology's Breast Cancer Symposium indicated this aromatase inhibitor continues to have a disease control advantage over tamoxifen long term. Arimidex showed an absolute 4.3% reduction in the hazard ratio for recurrence vs. tamoxifen, which was an even greater absolute difference than that seen at five years (2.7%). Importantly, the Arimidex patients did ***not*** have an excessive fracture risk, and no new morbidity or mortality concerns appeared.

P.L. THOMAS & COMPANY – potential new diet drug

P.L. Thomas has an agreement with **HGH Pharmaceuticals** for sceletium tortuosum, which comes from a plant that indigenous South Africans have chewed for decades to reduce stress, relieve hunger, sedate, and elevate mood. HGH has a license to study and market the drug and plans to sell it over-the-counter worldwide as a diet drug, and P.L. Thomas plans to launch it in the U.S. in 2011. *The question is what the FDA will think of this. It is likely to need FDA approval.*

ROCHE's MetMAb – no significant benefit with Tarceva in lung cancer

In preliminary Phase II data presented at ESMO, MetMAb + Roche's Tarceva (erlotinib) improved survival, but not significantly in advanced patients with high MET-expressing non-small cell lung cancer. In this randomized, double-blind, placebo-controlled study, patients' MET receptor expression status was scored by an immunohistochemistry (IHC) assay developed by Roche's Ventana division.

- Progression-free survival improved, but the difference did not meet statistical significance (p=0.0547).
- Median PFS improved from 6.4 weeks to 12.4 weeks.
- Overall survival (OS) improved, but again didn't meet statistical significance (p=0.1113).
- Median OS improved from 7.4 months to 7.7 months.

ROCHE/GENENTECH's Avastin (bevacizumab) – as effective as Lucentis in AMD study

A small study published in the journal ***Eye*** found that Avastin was as effective as Roche/Genentech's Lucentis (ranibizumab) in treating wet age-related macular degeneration (AMD). This was the first head-to-head study of the two drugs and could be a step toward FDA approval of Avastin for AMD, even without the company asking the Agency for approval.

SANOFI-AVENTIS's Plavix (clopidogrel) – maybe there isn't interaction with PPIs after all

There have been several reports that suggested that the proton pump inhibitors (PPIs) – particularly omeprazole – could interfere with the blood thinning action of Plavix, and the FDA changed the label for Plavix to warn of an increased cardiac risk with Plavix. However, a new article in the ***New England Journal of Medicine*** suggests that, based on test-tube studies, the risk may have been exaggerated.

SYNTHES – selling Norian unit

As part of its plea agreement with the Justice Department, Synthes is selling its Norian unit, which was alleged to have illegally tested (in 2002-2004) a bone cement for vertebral fractures that caused the deaths of three patients. Norian will plead guilty to a felony, pay a $23 million fine (plus another $700,000 to be paid by Synthes), and face exclusion from Medicare. The divestiture agreement was described as "unprecedented" in a healthcare fraud case. The bone cement is approved for use in the arm but not the spine. Norian and Synthes reportedly tested the product for unapproved uses but also failed to report the deaths to the FDA and lied to FDA investigators.

FDA NEWS

FDA's proposed 510(k) reform

The FDA is currently sorting through the comments it received on the proposed changes to the 510(k) approval process for medical devices. Dr. Sidney Wolfe, director of Public Citizen's Health Research Group, praised the efforts of Dr. Jeffrey Shuren, director of the FDA's Center for Devices and Radiological Health (CDRH) saying he is "capable of doing a better job than anyone who's ever been in there (CDRH)" even though the 510(k) process "is in need of major changes." However, the industry trade group – Advanced Medical Technology Association (AdvaMed) – described the changes as "potentially disruptive," urging the FDA to implement more limited changes.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	October 2010	
October TBA	**Allergan's Botox** (onabotulinumtoxinA) for chronic migraine	PDUFA date
October 11	**Jazz Pharmaceuticals' Rekinla** (JZP-6) for fibromyalgia	PDUFA date
October 12	**Alkermes' Vivitrol** (naltrexone ER injection) for opioid dependence	PDUFA date
October 18	**Safety and efficacy of erythropoiesis stimulation agents** (Amgen's Epogen and Aranesp and Johnson & Johnson's Procrit)	FDA's Cardiovascular and Renal Drugs Advisory Committee
October 19	**Boehringer Ingelheim's Pradaxa** (dabigatran), an anticoagulant	PDUFA date
October 21-22	**Design of post marketing studies** Purdue Pharma's newly reformulated OxyContin (oxycodone CR) and King/Alpharma's Embeda (morphine sulfate ER + naltrexone)	FDA's Anesthetic and Life Support Drugs Advisory Committee meeting jointly with the Drug Safety and Risk Management Advisory Committee
October 22	**Arena Pharmaceuticals/Eisai's lorcaserin**, a diet drug	PDUFA date
October 22	**Lilly/Amylin's Bydureon** (exenatide long-acting) for Type 2 diabetes	PDUFA date
October 24	**Warner Chilcott's Actonel delayed-release** (risedronate) for osteoporosis	PDUFA date
October 28	**Vivus's Qnexa** (phentermine + topiramate), a diet drug	PDUFA date
	November 2010	
November 2-3	Draft of regulations for **generic biologics**	FDA public hearing
November 16	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	FDA's Arthritis Advisory Committee
November 18	**Amgen's denosumab** for cancer patients	PDUFA date
November 18	**Mela Sciences' MelaFind** for melanoma detection	FDA's General and Plastic Surgery Devices Advisory Committee
November 30	**GlaxoSmithKline/Valeant's ezogabine** for epilepsy	PDUFA date
	December 2010	
December 2	**Oceana Therapeutics' Solesta** (dextranomer in gel of stabilized non-animal hyaluronate) for fecal incontinence	FDA's Gastroenterology and Urology Devices Advisory Committee
December 3	**Allergan's Lap-Band**	FDA's Gastroenterology and Urology Devices Advisory Committee
December 7	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
December 9	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	PDUFA date
December 16	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	Revised PDUFA date
December 25	**Bristol-Myers Squibb's ipilimumab** for advanced melanoma	PDUFA date
	Other future meetings	
January 7, 2011	**Endo Pharmaceuticals' tamper-resistant Opana ER** (oxymorphone), a painkiller	PDUFA date
January 31, 2011	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	PDUFA date
March 7, 2011	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	New PDUFA date
Date TBA, 2011	Review of **accelerated drug approval process**	FDA's Oncologic Drug Products Advisory Committee (ODAC)
Summer 2011	Report on **FDA 510(k) reform**	Institute of Medicine