Trends-in-Medicine

Quick Takes

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July 4, 2010

Happy Fourth of July!

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

SHORT TAKES

- **ABBOTT** is considering selling its Solvay vaccine unit, just a few months after buying Solvay in February 2010 for $6.2 billion. In 2009 Solvay sold $197 million in vaccines.
- **ALIMERA SCIENCES/PSIVIDA's Iluvien (sustained-release fluocinolone acetonide),** a back-of-the-eye insert, has been submitted to the FDA for approval to treat diabetic macular edema (DME).
- **ALNYLAM PHARMACEUTICALS' ALN-TTR –** Authorities in Portugal, Sweden, and the U.K. have given permission for the company to begin Phase I testing of this RNAi therapy for the treatment of transthyretin-mediated amyloidosis, a hereditary disease caused by a genetic mutation.
- **ARENA PHARMACEUTICALS' lorcaserin** will be sold by Eisai in the U.S. if and when the FDA approves the weight-loss drug. It will be reviewed by the FDA's Endocrinologic and Metabolic Drugs Advisory Committee on September 16, 2010. The PDUFA date is October 22, 2010.
- **ASTRAZENECA/MEDIMMUNE's motavizumab –** Following a negative advisory committee recommendation, the FDA delayed its decision until August 27, 2010, on this monoclonal antibody for the prevention of serious respiratory syncytial virus in infants.
- **CELGENE** is buying Abraxis BioScience for $2.9 billion in cash and stock.
- **COMPUGEN** discovered a protein that eradicated relapses of multiple sclerosis pain in rodents, and it may have utility in other autoimmune diseases.
- **ENDO PHARMACEUTICALS' Fortesta (testosterone gel) –** The company provided the FDA with additional information the Agency had requested from a new analysis of a prior study. An FDA decision is expected by the end of the year.

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- **EVOTEC/ROCHE's EVT-101 –** A proof-of-concept trial in treatment-resistant depression is underway in the U.S. for this NR2B subtype selective NMDA receptor antagonist. It is an ~100-patient, 4-week, Phase II safety and tolerability study.

- **GENMAB/GLAXOSMITHKLINE's ofatumumab –** In a change in development responsibilities, GSK will now be responsible for developing ofatumumab in autoimmune indications, and the two companies will jointly develop ofatumumab in oncology indications.

- **MEDTRONIC** received a warning letter from the FDA relating to complaint handling and device reporting at its Surgical Technologies plant in Louisville CO. The plant makes hardware and software for use during surgical procedures. In other news, a U.K. court ruled that Medtronic's CoreValve percutaneous aortic valve does not infringe Edwards Lifesciences heart valve patents.

- **MYRIAD PHARMACEUTICALS** is now officially **MYREXIS**. The name change became official July 1, 2010.

- **PAIN THERAPEUTICS and KING PHARMACEUTICALS' Remoxy (oxycodone controlled-release) –** Pain Therapeutics has modified its strategic alliance with King for Remoxy in Europe. King will now make a one-time $5 million payment to Pain Therapeutics in July 2010 and then pay Pain Therapeutics a 10% royalty on net European sales. The royalty rate in the U.S. and U.S. milestone payments are unchanged. Pain Therapeutics also said that resubmission of Remoxy to the FDA is still anticipated in 4Q10.

- **SHIRE PHARMACEUTICALS' Intuniv (guanfacine) –** The FDA warned Shire that it was overstating the benefits of this extended-release ADHD (attention-deficit/hyperactivity disorder) drug in marketing materials by making "unsubstantiated effectiveness claims" and omitting and minimizing risk information.

- **VALEANT/GSK's Potiga (ezogabine, formerly retigabine) –** An FDA advisory committee will review this K-channel modulator for epilepsy on August 11, 2010. The questions may focus on urinary retention (hesitation) in some patients (~6% with 1200 mg).

NEWS IN BRIEF

Alzheimer's disease – study indicates best predictors

Patients with mild cognitive dysfunction who have abnormal PET scans and who score poorly on episodic memory tests are 12 times more likely to go on to develop Alzheimer's disease vs. other mild cognitive dysfunction patients. The results of a substudy of the Alzheimer's Disease Neuroimaging Initiative were reported in the June 30, 2010, online issue of ***Neurology***.

Other evaluation methods reviewed included the presence of the apoE gene, MRI scans, levels of tau protein, and the amount of beta-amyloid. Although these parameters have previously been shown useful to predict disease progression, they were not as predictive as PET scans and memory test scores when all of the measures were compared to each other in the same study.

BIOSENSORS – buying small vessel stent systems from CardioMind

The Sparrow stent system has a 0.014-inch guidewire-based stent delivery platform. The bare-metal version has a CE Mark for treating small vessels; the drug-eluting Sparrow combines sirolimus in a biodegradable polymer matrix.

Breast cancer – high medication non-adherence

A new study of nearly 8,800 women with early-stage breast cancer found that fewer than half (~49%) completed their full regimen of hormone therapy – e.g., tamoxifen or an aromatase inhibitor – according to the prescribed schedule. The study, published in the ***Journal of Clinical Oncology***, looked at pharmacy records for 8,769 breast cancer patients. Other findings included:

- Women <age 40 and >age 75 were more likely to discontinue therapy early.

- By 4.5 years, 32% of patients had stopped taking their hormone therapy, and of those who did not stop, only 72% finished on schedule (meaning they took their medication >80% of the time).

- Women with a lumpectomy were more likely to discontinue therapy than women who had a mastectomy.

CHELSEA THERAPEUTICS's Northera (droxidopa/carbidopa) – positive interim results in Phase II fibromyalgia trial

An independent Data Monitoring Committee (DMC) reviewed efficacy data from ~50% of the target enrollment in a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 9-week, Phase II, dose-finding trial and determined that 7 of the 12 arms should continue: placebo, 50 mg carbidopa TID, 600 mg droxidopa TID; 400/25 mg, 200/50 mg, 400/50 mg, or 600/50 mg. The primary endpoint in the trial is a reduction in pain on the Short Form McGill Pain Questionnaire. No safety concerns or significant adverse events were found in any treatment arm. For the company, this means the three key combinations are 200/50, 400/50 and 600/50. Thus, the study is now focusing primarily on multiple doses of droxidopa in combination with 50 mg carbidopa. Top line data from this study is expected by the end of 2011.

Congress
– investigating pharma treatment of whistleblowers

Sen. Charles Grassley recently sent letters to 16 drug companies asking them to explain in writing by July 20, 2010, how they treat whistleblowers who file complaints under the Medicare False Claims Act. The letter asked the companies to respond to 8 questions, including: how they notify employees about the law, how they treat whistleblowers, how they ensure whistleblowers are treated fairly, and how they have responded to new anti-retaliation protections. According to ***Bloomberg***, the Justice Department is investigating nearly 1,000 whistleblower cases filed under seal.

Continuous-flow left ventricular assist devices (LVADs)
– increased risk of bleeding

The newer, continuous-flow LVADs appear to have a higher rate of thromboembolic events than the older pulsatile devices. While the anticoagulants that continuous-flow device users must take could contribute to the increased bleeding, it doesn't explain all of it. In an article in the ***Journal of the American College of Cardiology***, researchers urged a randomized, multicenter, prospective trial be conducted to find the best anticoagulation regimen for these patients.

DENDREON's Provenge (sipuleucel-T)
– CMS review to take a year

The Centers for Medicare & Medicaid Services (CMS) has opened a national coverage decision (NCD) to review this prostate cancer immunotherapy and determine whether it will cover treatment. Some Medicare providers are currently paying for Provenge, and they can continue to do so during the CMS review, which is expected to yield a proposal in nine months and a final decision in a year. A 30-day public comment period began June 30, 2010, and another public comment period will be held after the proposal is issued.

CMS will also be deciding what Provenge is, exactly. Although it has been touted as a vaccine, it is not one because it does not prevent the disease. Instead, a patient's blood is mixed with Provenge, which boosts the immune system and attaches to the patient's specific cancer cell proteins. Therefore, Provenge is not a typical biologic agent either, and it is not a traditional drug. Because the amount of CMS coverage varies according to the type of agent, what the Agency decides Provenge is will be of interest.

Provenge, which costs $93,000 for a course of treatment, received FDA approval in April 2010 for men with metastasizing prostate cancer that does not respond to hormone therapies. In clinical trials, Provenge extended survival by 4 months in these patients.

Down syndrome – possible treatment for cognitive deficits

It was assumed that Down syndrome (DS) is synonymous with intellectual disability, but that may not be true. Two recent papers suggested that it may be possible to develop a treatment for the cognitive deficits of Down syndrome. The researchers found that amyloid-beta (Aβ), which plays a role in Alzheimer's disease, also has a key role early in Down syndrome. In an article in ***PLoS One***, Dr. Paul Greengard of Rockefeller University and colleagues reported that learning deficits could be reversed in a Down syndrome mouse model by lowering the levels of soluble Aβ in the brains of young mice. In another article in the same journal, Dr. Lee Goldstein of Boston University and colleagues reported that the characteristic cataracts seen in Down syndrome are composed of Aβ aggregates, and these cataracts may be one of the earliest signs of Aβ accumulation in a person with Down syndrome. These findings suggest that researchers may find early diagnosis and treatment options for the cognitive deficits of Down syndrome.

FOREST LABORATORIES' radiprodil (RGH-896)
– fails pain study goals

The company and partner Gedeon Richter said that radiprodil failed to meet key goals in a Phase II trial in patients with pain due to diabetic neuropathy. The companies said they will review the complete trial results during the next several weeks to determine what additional drug development steps will be.

Gastric banding
– deteriorating, modest weight loss reported

Two-thirds of patients undergoing adjustable gastric banding maintained a 25% excess weight loss 5 years after the procedure, and only 31% achieved the same maintenance after 10 years, according to results of a study reported during the American Society of Metabolic and Bariatric Surgery meeting. If the desired standard of a 40% excess weight loss is used, there was a 5-year success rate of 50% and a 10-year success rate of 20%.

The researchers reviewed 201 cases of laparoscopic banding in The Netherlands between 1995 and 2003 and followed the patients for a mean of 9.6 years. They found that a third of patients required reoperation after 5 years, and 53% required reoperation after 10 years. Not only did weight loss maintenance decline over time, the control of obesity-related comorbidities, including diabetes, hypertension, and gastroesophageal reflux did as well. The Dutch researchers said that the hospital was reevaluating the use of the procedure.

GENZYME – more supply issues

While supplies of Cerezyme (imiglucerase) for Gaucher's disease are expected to increase after July, the company is still saying there will be "short-term shipping delays." And Genzyme now is warning of short-term delays of Fabrazyme

(agalsidase beta), due to lower than expected production levels. The company said it is working on Fabrazyme production, but supplies will remain at the current level for the next three months.

GLAXOSMITHKLINE's Avandia (rosiglitazone) – opinions mixed on outlook

An FDA advisory committee will consider the fate of this oral Type 2 diabetes drug on July 13 and 14, 2010, but a poll by ***MedPageToday*** found that ~40% of respondents believe it should be pulled from the market, while ~32% believe it should be kept available with restrictions, and ~19% voted that a decision should await the results of a randomized safety study. Only ~9% thought the concerns are overblown.

H1N1 flu – possible new vaccine approach

In an article in the ***Proceedings of the National Academy of Sciences***, a team of researchers from the University of Wisconsin-Madison and Theraclone reported on rare antibodies that the body makes which are effective against all flu viruses. They suggested these antibodies –which were identified by Theraclone, which contracted with the university to make them in quantity and test them in mice – might be boosted to design a better universal flu treatment, one that could help most people survive a normally deadly flu virus. Researcher Dr. Yoshihiro Kawaoka said, "The ability of these antibodies to protect mice from highly lethal strains of influenza is encouraging."

HRA PHARMA's EllaOne (ulipristal acetate) – possible treatment for uterine fibroids

Researchers at the European Society of Human Reproduction and Embryology meeting reported that this drug, which is used in Europe as an emergency contraceptive, may also treat painful uterine fibroids. They studied 57 women with symptomatic fibroids, and after many women took the drug QD for three menstrual cycles, they showed reductions in the size of their fibroids and no menstrual bleeding (80% of patients at 10 mg and 95% at 20 mg).

Imaging – CMS reviewing MRIs for patients with cardiac devices

CMS is asking for public comment on the use of MRI in clinical trial participants who have pacemakers or implantable ICDs. CMS is reconsidering its National Coverage Determination for the test, which currently is contraindicated for patients with cardiac devices. The agency is looking at whether to provide coverage if the MRI is clinically indicated and performed as part of a prospective clinical trial on the risk of the procedure and/or the study is conducted after an IDE has been approved by the FDA for the proposed research. CMS is accepting comments until July 28, 2010, and will issue a proposed decision memo by December 28, 2010.

LILLY's Effient (prasugrel) – linked to higher cancer risk

A study reported in the ***Archives of Internal Medicine*** found that Effient patients had a 43% higher rate of solid tumors, excluding some skin cancers and brain tumors, than patients on Sanofi-Aventis's Plavix (clopidogrel). And the risk is much higher than previous data from the pivotal trial (TRITON-TIMI-38) suggested.

Never-published data from the pivotal TRITON-TIMI-38 trial of Effient vs. Plavix suggested that the risk of new or worsened solid-tumor cancers was increased 62% with prasugrel (p=0.001). An investigator, Dr. James Floyd from the University of Washington, said, "The main message to the FDA is, let's make sure this thing doesn't cause cancer if you're going to keep it on the market."

In an accompanying editorial, Dr. Sanjay Kaul and Dr. George Diamond, both from UCLA, called for a boxed warning on Effient and duration of use should be limited, "We believe... prasugrel use should be limited to a duration of weeks rather than months."

mTOR inhibitors – fail to stop renal decline

Novartis' Zortress and Afinitor (everolimus) and Pfizer/Wyeth's Rapamune (sirolimus) did not stop declining kidney function in patients with autosomal dominant polycystic kidney disease (ADPKD), according to results of two separate trials reported in the ***New England Journal of Medicine***. Everolimus slowed increasing kidney volume but did not improve glomerular filtration rate (GFR) in patients with ADPKD and mid-stage kidney dysfunction, in one study. In a smaller study in patients with less advanced ADPKD, sirolimus did not slow kidney volume or improve GFR compared with placebo.

In an accompanying editorial, Dr. Terry Watnick of Johns Hopkins University and Dr. Gregory Germino of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) wrote, "Taken together, these studies suggest that therapy with these mTOR inhibitors will not be the sought-after magic bullet, regardless of ADPKD stage."

Multiple sclerosis – blocked blood veins may *not* be the cause

New research from Germany refutes the results from a 300-patient Italian study last year which suggested that chronic cerebrospinal venous insufficiency is the cause of MS. The Italian researchers had studied 300 patients using ultrasound and found that nearly all the MS patients had obstructed blood flow in veins exiting the brain while none of the controls did. The theory is that stenosis of the veins leaving the brain cause blood to back up, leading to inflammation. The findings were controversial but intriguing.

The German researchers performed ultrasound examinations of the jugular and vertebral veins of 56 MS patients and 20 controls, and they found no difference between the two groups. Only one MS patient and no controls had obstructed blood flow in jugular or vertebral veins. Their findings were published online in ***Annals of Neurology***.

This is the second study to refute the Italian findings.

Platelet reactivity testing
– doctors looking for alternatives to genetic testing

A ***CRTonline.org*** survey found that to determine patient responsiveness to antiplatelet therapy, 38% of cardiologists use platelet reactivity testing, 6% do genetic testing, 44% do not test at all, and 13% do both genetic and platelet reactivity testing.

The FDA has recommended genetic testing for patients taking Sanofi-Aventis's Plavix (clopidogrel), but that isn't always easy. In an article in the ***Journal of the American College of Cardiology: Cardiovascular Interventions***, French researchers reported that some patients may have genetic mutations which don't allow Plavix to work effectively and that genetic testing is not always an easy option. Researchers determined that a vasodilator-stimulated phosphoprotein flow cytometry (VASP-FCT) specific to P2Y12 can simply and easily predict patients at high risk of cardiovascular death following percutaneous coronary intervention (PCI).

The researchers assessed 461 patients in a prospective registry using VASP-FCT and found lower platelet reactivity index (PRI) scores were associated with higher antiplatelet efficacy. They set a cutoff PRI threshold of 61%. At 9 months, the patients with a high PRI score had higher cardiac mortality rate (HR 4.0) and more stent thrombosis. The cutoff threshold for VASP tests has not been uniform, but these researchers found that their threshold of 61% clearly identified those at high risk.

In an accompanying editorial, Dr. Sotirios Tsimikas and Dr. Gregor Leibundgut, both of the University of California, San Diego, wondered whether there is need for genetic testing with the approval of Lilly's Effient (prasugrel) and with new agents on the horizon, such as AstraZeneca's Brilinta (ticagrelor), "Although prasugrel is associated with better efficacy and also more bleeding, ticagrelor demonstrated reduced cardiovascular mortality with similar bleeding rates. With clopidogrel becoming available as a generic drug soon, cost issues might ultimately drive the debate about when and if to genotype or measure platelet function."

Radiology – CMS cutting reimbursement

Using a new formula, CMS is cutting reimbursement to radiologists and will pay less per CT or MRI scan in 2011 than in 2010. In addition, CMS cut payments July 1, 2010, for scans on consecutive parts of the body, reducing those payments by 25% of the least expensive scan. Next year, CMS plans to make the reduction for the second scan 50%. And the agency is proposing applying the "discount" to multiple scans that are ***not*** on consecutive parts of the body (e.g., a hand and a foot).

ROCHE/GENENTECH's Avastin (bevacizumab)
– more positive data in ovarian cancer

A second large, international Phase III study found that Avastin 7.5 mg/kg + chemotherapy (carboplatin + paclitaxel) increased progression-free survival (PFS) in women with previously untreated ovarian cancer vs. chemotherapy alone, with no new or unexpected adverse events. ICON7, which was sponsored by the U.K.'s Medical Research Council (MRC), was a multicenter, randomized, open-label study of 1,528 women with newly diagnosed ovarian cancer (both advanced and earlier stage disease) who had already had surgery.

The results of the first Phase III trial (GOG-0218) were presented at ASCO 2010, and it also met its primary endpoint, showing a statistically significant increase in PFS in women with advanced ovarian cancer with a higher Avastin dose (15 mg/kg) + the same chemotherapy regimen.

SPECTRANETICS
– some thrombus extraction catheters recalled

Some lots of the company's thrombus extraction catheter have been recalled because of a manufacturing issue that may cause a blocked guidewire lumen that restricts loading the catheter onto the guidewire prior to insertion. Spectranetics said no adverse effects have been reported but that it has received customer complaints. The company will replace the recalled units.

SUPERGEN/EISAI's Dacogen (decitabine injection)
– failed in a Phase III trial in AML

Dacogen already is approved to treat myelodysplastic syndrome, but it failed to show superiority to control on the primary endpoint (overall survival) in a Phase III trial in acute myeloid leukemia (AML), though there was a "trend" to a better outcome with Dacogen. However, Eisai still reportedly plans to file for a leukemia indication by March 31, 2011. Among the adverse effects reported in the trial were: sepsis, febrile neutropenia, anemia, fever, thrombocytopenia, and pneumonia.

VARIAN MEDICAL SYSTEMS
– expanding its partnership with Brainlab

Varian is incorporating its Novalis technology and other Novalis Radiosurgery Program elements with Brainlab's recently launched TrueBeam STx system. The expanded suite of products will be called "Novalis powered by TrueBeam STx." The announcement was made at the 5th International

Conference of the Novalis Circle, a meeting in Munich, Germany, of Novalis radiosurgery users.

FDA News

Latest drugs under safety review

The FDA has initiated a safety review of several drugs, including:

- **Cubist Pharmaceuticals' Cubicin** (daptomycin for injection), an antibiotic – for reports of a type of pneumonia.
- **Jazz Pharmaceuticals' Xyrem** (sodium oxybate), a sleep disorder drug – for a possible new adverse event, "convulsion."
- **Lilly/Daiichi Sankyo's Effient** (prasugrel), a platelet inhibitor – for 1-2 cases of thrombotic thrombocytopenic purpura (TTP), a rare but potentially fat blood disorder, since it was approved. A label change is in the works.
- **Sanofi-Aventis's Multaq** (dronedarone), an antiarrhythmic – for reports of congestive heart failure.

Stimulant safety study

A study by the FDA and the U.S. Department of Health and Human Services (HHS) on the safety of attention-deficit/hyperactivity disorder (ADHD) medicines that use stimulants, such as amphetamines, is due this August. That study was launched in 2007 over concerns about potential cardiovascular problems with the drugs. ♦

Upcoming FDA Advisory Committees of Interest ***(items in red are new since last week)***

Date	Topic	Committee
	July 2010	
July 13-14	**GlaxoSmithKline's Avandia** (rosiglitazone) cardiovascular safety – and to a lesser extent the safety of **Takeda's Actos** (pioglitazone)	Joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee ***and*** the Drug Safety and Risk Management Advisory Committee
July 15	**Vivus's diet drug Qnexa** (phentermine + topiramate)	Endocrinologic and Metabolic Drugs Advisory Committee
July 19-20	**Oversight of laboratory-developed tests**, especially genetic tests	Public meeting
July 20	**Roche/Genentech's Avastin** (bevacizumab) – two supplemental BLAs for naïve metastatic HER2-negative breast cancer	Oncologic Drugs Advisory Committee (ODAC)
July 22-23	**REMS for long-acting opioids**	Joint meeting of the Anesthetic and Life Support Drugs Advisory Committee ***and*** the Drug Safety and Risk Management Advisory Committee
July 27-28	Meeting to obtain input on issues and challenges associated with the development and implementation of risk evaluation and mitigation strategies (**REMS**)	Public hearing
July 28	**AstraZeneca's Brilinta** (ticagrelor)	Cardiovascular and Renal Drugs Advisory Committee
July 30	**Glaukos's iStent Trabecular Micro-Bypass Stent** for treating open-angle glaucoma during cataract surgery	Ophthalmic Devices Advisory Committee
	August 2010	
August 11	**Valeant/GSK's Potiga (ezogabine, formerly retigabine)** for epilepsy	Peripheral and Central Nervous System Drugs Advisory Committee
August 20	**Jazz Pharmaceuticals' Xyrem** (sodium oxybate, JZP-6) for fibromyalgia	Arthritis Advisory Committee joint meeting with the Drug Safety and Risk Management Advisory Committee
August 26	**Mela Sciences' MelaFind**, an optical device for melanoma detection	General and Plastic Surgery Devices Advisory Committee
	September 2010	
September 16	**Arena Pharmaceuticals' locaserin** diet drug	Endocrinologic and Metabolic Drugs Advisory Committee
September 17 (not confirmed)	**Boehringer Ingelheim's Pradaxa** (dabigatran)	Cardiovascular and Renal Drugs Advisory Committee