Trends-in-Medicine

Quick Takes

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

SHORT TAKES

- **ABBOTT LABORATORIES** canceled plans to sell its European flu vaccine subsidiary after initial bids were below its expectations. It now plans to integrate the unit into its other operations.
- **ALIMERA SCIENCES' Iluvien (sustained-release fluocinolone acetonide)** received priority review status from the FDA for treating diabetic macular edema (DME). The company expects an FDA decision in 4Q10.
- **ALLERGAN** settled the Department of Justice's investigation into alleged off-label sales and marketing of Botox (onabotulinumtoxinA) by paying a $600,000 fine – $375,000 for misbranding and $225,000 to resolve civil claims. The company also agreed to a five-year corporate integrity agreement (CIA) with the Office of the Inspector General (OIG) to maintain its current marketing compliance program. *This may sound simple, but CIAs are onerous, not easy.*
- **Anesthesia shortage** – A nationwide shortage of several anesthesia drugs is causing some hospitals to postpone elective surgeries. Bona Benjamin of the American Society of Health-System Pharmacists said that anesthesiologists "are being very challenged right now." **Hospira**, the only U.S. manufacturer of sodium thiopental, said that manufacturing problems are to blame for shortages of that drug.
- **Anthracyclines** – Only about a quarter of breast cancer patients respond to this chemotherapy agent. However, the Institute for Cancer Research in London has developed a test that may help identify who the responders will be by measuring the levels of RAD51 in biopsy tissue.
- **ASTRAZENECA's Seroquel (quetiapine)** – Some military families are asking for a Congressional investigation of the Veterans Administration's use of this anti-psychotic drug to treat post-traumatic stress disorder (PTSD). Seroquel has been prescribed to thousands of soldiers suffering from PTSD to treat their insomnia, and it is one of the VA's most prescribed drugs, but it is not FDA approved to treat insomnia, and several soldiers and veterans have died while taking it.

- **ASTRAZENECA/MEDIMMUNE's motavizumab** – The FDA wants another study showing a satisfactory risk:benefit profile in the target population before approving this drug to prevent respiratory syncytial virus (RSV).

- **BAUSCH + LOMB** said that it concluded its acquisition of a portion of the assets and intellectual property for Miochol-E (acetylcholine chloride intraocular solution) from Affiliates of Novartis AG. The company finished its purchase in the U.S., Canada, Australia, and Korea, along with some other markets outside of the European Economic Area.

- **BAXTER's Aralast NP** – The company received a warning letter from the FDA for "misleading statements" in a brochure for this lung drug. The company has put the promotional materials on hold. Baxter was cited for similar violations in April 2009 and July 2008.

- **BIOMARIN's BMN-701** received orphan drug status for Pompe disease treatment from the FDA. The company plans to start clinical trials in 1Q11.

- **BIOVEDA's BAX 3000** – The FDA sent the company a warning letter saying that the company sold BAX 3000, a biofeedback machine approved for relaxation training, for uses not approved by the FDA, including for the treatment of allergies and neurological disorders. A spokesman for BioVeda said that the warning letter incorrectly identified the company as the manufacturer of the device and said that the company stopped selling the product before it received the notice.

- **COLLPLANT's Vergenix** – The FDA determined this wound-healing product, a recombinant human collagen scaffold, is a medical device and is subject to review by the Center for Devices and Radiological Health (CDRH).

- **ELITE PHARMACEUTICALS** is buying **Mikah Pharma**'s FDA-approved naltrexone hydrochloride 50 mg tablets. The brand product and its generic equivalents had annual sales of ~$14 million in 2009. There are three other approved generic manufacturers plus the innovator. Elite expects to start manufacturing the product early in 2011 and will sell the drug in the U.S. and its territories; Mikah has the right to sell the drug in the rest of the world. Elite is also working with Mikah to develop a new product.

- **FOREST LABORATORIES** and **GEDEON RICHTER's cariprazine** failed to show a statistically significant benefit over placebo in a Phase II study in bipolar depression. However, the companies said there was a "clinically relevant" result with the highest dose, so it will be studied further.

- **FRESENIUS BIOTECH's Removab (catumaxomab)** may be effective against malignant ascites. The drug is the first causal therapy against malignant ascites approved by the European Commission. At the Union for International Cancer Control (UICC) World Cancer Congress, researchers in Germany presented data culled from a Phase I/II trial showing that catumaxomab, in a series of four intraperitoneal infusions, resulted in a clinical benefit in the treatment of symptomatic malignant ascites.

- **GILEAD** may get a warning letter from the FDA for maintenance and procedural problems that were found during an inspection at its California facility, the only site where its fungal treatment AmBisome (amphotericin) and Cayston (aztreonam), an inhaled antibiotic for cystic fibrosis, are made.

- **GLAXOSMITHKLINE/VALEANT PHARMACEUTICALS' ezogabine** – The FDA extended its review of this potential epilepsy drug until November 2010. The companies recently submitted a plan of risk evaluation and mitigation for the treatment.

- **HALOZYME THERAPEUTICS** finished investigating how glass particles ended up in some vials of Hylenex, a fluid-absorption drug recalled by manufacturing partner **Baxter** in May 2010. The investigation found that the drug and the glass vial were incompatible. The companies plan to present their corrective action and relaunch strategy to the FDA.

- **HANSEN MEDICAL's Sensei X CoHesion** 3-D visualization module will be integrated with **St. Jude's EnSite Velocity** cardiac mapping system. The two companies signed an agreement to combine commercialization of the two complementary electrophysiology products in the U.S. and Europe.

- **MACROGENICS' MGAWN1** – The National Institutes of Health (NIH) is giving $50 million to help develop therapies for West Nile virus. Rush University Medical Center, an NIH testing site, is looking for participants to join the clinical trials for MGAWN1, which are being conducted at 25 sites in the U.S., mostly in western states, where West Nile has been most prevalent.

- **MERCK's Brinavess (vernakalant)** – The intravenous formulation of Brinavess has approval in Europe, Iceland, and Norway for the rapid conversion of recent onset atrial fibrillation (AFib) to sinus rhythm in adults, for non-surgery patients with AFib of ≤7 days, and for post-cardiac surgery patients with AFib of ≤3 days.

- **NOVARTIS's NITD-609** cured mice of malaria at lower doses than existing medicines and killed drug-resistant strains taken from patients in Thailand, researchers reported in the journal ***Science***. Human trials could begin later in 2010.

- **OREXIGEN THERAPEUTICS' Contrave (bupropion SR/naltrexone SR)** – Orexigen is partnering with **Takeda** to market this obesity medication. This is the fourth obesity drug Takeda has bought or licensed since 2004.

- **PFIZER** is buying privately-held **FoldRx Pharmaceuticals**, which is developing drugs to treat diseases caused by protein misfolding, including tafamidis meglumine for TTR amyloid polyneuropathy.

- **SANOFI-AVENTIS's teriflunomide,** an oral drug for multiple sclerosis, met the primary endpoint in a Phase III trial, significantly reducing the relapse rate vs. placebo. The full results of that study will be presented in October 2010 at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Gothenburg, Sweden.

- **SERVIER's ivabradine** cut the heart rate and improved outcomes in heart failure patients in the SHIFT trial, which was presented at the European Society of Cardiology and simultaneously published in ***The Lancet***. Ivabradine is approved in Europe but not the U.S., and it is unlikely it will be submitted to the FDA based on this data, especially after the failure last year of the BEAUTIFUL trial. An accompanying editorial in ***The Lancet*** noted that the positive results in SHIFT may have been due, at least in part, to patients not being on maximum doses of beta blockers.

- **STROMEDIX's STX-100** received orphan drug designation from the FDA for the treatment of idiopathic pulmonary fibrosis. The company plans to start a Phase II trial in 2011.

- **STRYKER** bought the ulcer management business of privately-held **Gaymar Industries**.

- **SUN PHARMA** received an FDA warning letter about manufacturing violations at a plant in Cranbury NJ. The Indian drugmaker said that regulatory approval has been delayed for products from the facility, but it does not expect the matter to harm its U.S. operation.

- **Vaccines –** A federal appeals court upheld a ruling last year by a special vaccine court that vaccines are not to blame for autism.

- **ZIMMER's NexGen LPS-Flex –** A Korean study of 85 women found this gender-specific knee replacement provided no clinical benefits vs. a standard Zimmer knee. The study, which was published in the ***Journal of Bone and Joint Surgery***, examined women ≥2 years after surgery and found the two knees had similar knee score, similar range of motion, and similar patient satisfaction. In fact, the researchers reported that the standard knee fit the distal part of the femur better than the gender-specific prosthesis.

NEWS IN BRIEF

ABBOTT's Meridia (sibutramine) – increased risk of strokes and heart attacks

A study published in the ***New England Journal of Medicine (NEJM)*** found that among nearly 10,000 overweight or obese patients, those on Meridia had a 16% greater risk of having a heart attack or stroke over three to four years vs. patients on placebo. None of the events was fatal, but the results were concerning because the trial only included patients with a previous history of heart disease, diabetes, or both. In an accompanying editorial, ***NEJM*** executive Dr. Gregory Curfman said, "With sibutramine we have a risk:benefit picture that is not favorable…In my opinion, it's time for regulatory action on the drug." An FDA advisory committee is scheduled to review Meridia on September 15, 2010.

Dr. Sidney Wolfe, director of the non-profit Public Citizen's Health Research Group, said that the study was no surprise. His group wants the FDA to ban Meridia for two reasons: (1) because in pre-approval randomized trials it "significantly increased heart rate and blood pressure, both risk factors for heart attacks and strokes," and (2) because the FDA's 1996 advisory committee "voted narrowly against its approval" and was "also opposed by the FDA medical officer reviewing the drug. By 2002…cases of otherwise unexplained heart attacks in young Meridia users had been reported to the FDA… (which) appears immobilized to act against drugs without any unique benefits but unique, serious dangers."

Alzheimer's disease – two potential new treatment targets

1. **GSAP.** A researcher has discovered a potential new target in treating this disease, gamma secretase activating protein (GSAP), which tells gamma secretase to make beta amyloid. The mouse finding was reported in an article in the journal ***Nature***. Paul Greengard, PhD, a Nobel Prize winning neuroscientist from Rockefeller University, reported that when the gene for GSAP was blocked in the mice, they did not develop the beta-amyloid brain plaques characteristic of Alzheimer's. A goal will be a drug that can bind to GSAP ***and*** cross the blood brain barrier. Modified forms of Novartis's Gleevec (imatinib), for example, can bind to GSAP, but Gleevec does not cross the blood brain barrier.

2. **Angiogenesis.** Perhaps stimulating angiogenesis in the brain would help Alzheimer's patients. That's one suggestion arising from a study in the ***Journal of Neuroscience*** by Dr. Michael Mullan of the Roskamp Institute in Florida. Several studies have shown that Alzheimer's patients appear less susceptible to cancer, but the mechanism of action was unknown. Dr. Mullan found that AD mouse brains were anti-angiogenic, perhaps due to soluble beta-amyloid in their brains. Other researchers are now speculating that stimulating brain vascularization could be beneficial in Alzheimer's patients and be a treatment approach.

Amyotrophic lateral sclerosis (ALS) – may be a mitochondrial channelopathy

Researchers from the University of California, San Diego, reported in the journal ***Neuron*** that ALS may be a mitochondrial channelopathy, due to misfolding of an enzyme. They showed that the misfolded enzyme poisons motor neurons by plugging up pores in their mitochondria, shutting down the voltage-dependent anion channel VDAC1 (mitochondrial porin), so less ADP gets into the mitochondria, and they produce less ATP, which could damage cells. Thus, VDAC1 may be a potential drug target in ALS.

Bisphosphonates – may increase esophageal cancer risk

A new study by Oxford researchers found that bisphosphonates may increase the risk of contracting cancer of the esophagus. Patients who took bisphosphonates for five years and filled at least 10 prescriptions were twice as likely to be diagnosed with the cancer as those who didn't. The findings are in contrast to a study published recently in the ***Journal of the American Medical Association (JAMA)*** that used the same database of 80,000 patients and which concluded that there was no link between the drugs and esophageal cancer.

Breast cancer – possible non-toxic molecular therapy

A University of Arizona researcher believes that she has found a non-toxic molecular therapy for triple-negative breast cancer. Joyce Schroeder, PhD, has a patent for PMIP (protein transduction domain 4 MUC1 inhibitory peptide), which is a small slice of MUC1 that causes EGFR to degrade. PMIP works in animals, and she is now seeking funding for human clinical trials.

Electronic health records (EHRs)

1. **Adopted in fewer than 12% of U.S. hospitals.** A hospital survey found that only 11.9% of U.S. hospitals had adopted EHRs as of the end of 2009. The study, which was published in ***Health Affairs***, also found that only ~2% of hospitals had met the federal criteria for meaningful use, which would enable them to get government incentives.
2. **Certifying bodies chosen.** The Department of Health and Human Services (HHS) named two groups that will be in charge of certifying which EHRs meet the federal government's standards for "meaningful use" – Chicago-based Certification Commission for Health Information Technology (CCHIT) and Drummond Group in Austin TX. Additional certification bodies may be added in the future.

J&J's tapentadol ER – Phase III study shows promise for knee pain

A positive Phase III study of tapentadol ER showed that it may be effective in the treatment of moderate-to-severe osteoarthritis knee pain. The study, which randomized 1,023 patients to oral tapentadol ER, oxycodone HCl CR, or placebo during a 15-week, double-blind period, showed that a significantly higher percentage of patients taking tapentadol ER achieved ≥50% improvement in average pain intensity vs. placebo (32% vs. 24.3%).

Phase III Results with Tapentadol ER in Osteoarthritis of the Knee Pain

Measurement	Tapentadol ER	Placebo
>50% improvement in average pain intensity	32%	24.3%
Treatment-emergent adverse events		
Any	75.9%	61.1%
Gastrointestinal	7.3%	1.8%
Nausea	21.5%	N/A
Constipation	18.9%	N/A
Vomiting	5.2%	N/A
Somnolence	10.8%	N/A
Dizziness	17.7%	N/A
Headache	14.8%	N/A
Fatigue	10.8%	N/A
Pruritis	7.0%	N/A
Discontinuations due to treatment-emergent adverse events		
Any	19.2%	6.5%
GI	7.3%	1.8%
Nausea	4.1%	N/A
Constipation	1.7%	N/A
Vomiting	1.2%	N/A

Opioid painkiller addiction – major risk factors identified

A 705-patient study published in the journal ***Addiction*** said that among back pain patients who were prescribed opioid painkillers for more than three months, the group most vulnerable to addiction had four main risk factors in common: age <65, a history of depression, prior drug abuse, and use of psychiatric medication. The study found that painkiller addiction rates among patients with these factors were as high as 26%.

OVATECH's Ovaprene – positive Phase II results

Ovaprene is a "one-size-fits-all," organic, non-hormonal, intravaginal, silicone contraceptive ring – a barrier-contraceptive – designed to continuously release spermiostatic and spermicidal non-drug agents over a four-week period. In a 3-month, 85-patient Phase II trial, all the rings remained in place, and >300 post-coital tests of the women's cervical pool showed zero motile sperm. The women – and their partners – said they liked the product.

PFIZER's Tygacil (tigecycline) – FDA warns of increased mortality risk

The FDA reminded healthcare professionals of an increased mortality risk associated with the use of this intravenous antibacterial agent used to treat a variety of serious infections. The FDA said the increased risk was seen most clearly in patients treated for hospital-acquired pneumonia, especially ventilator-associated pneumonia, but was also seen in patients with complicated skin and skin structure infections, complicated intra-abdominal infections, and diabetic foot infections. The FDA updated sections of the Tygacil label to include information about an increased mortality risk. Tygacil is approved for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired pneumonia. It is not approved for treatment of hospital-acquired pneumonia or diabetic food infection.

SPECTRANETICS – former executives indicted

Three former Spectranetics executives and a company representative were named in a 12-count federal indictment charging conspiracy, false statements, importation violations, introduction of adulterated and misbranded medical devices, and receipt of adulterated and misbranded medical devices. The indictments were announced by the U.S. Attorney's Office in Colorado and by the FDA Office of Criminal Investigations. Arrests are expected.

Indicted were George Schulte, who resigned as CEO in October 2008; Larry Adighije, former vice president of Business Development; Trung Pham, a fomer business development manager; and Hernan Ricaurte, who had been a representative of BAC, a corporation contracted to identify potential sourcing partners for the company's medical products.

The indictment alleges that from January 2004 through October 2008 the defendants conspired to obstruct and defeat the law function of the FDA and U.S. Customs and Border Protection, specifically the inspecting, taxing, evaluating, and clearing of medical devices imported into the U.S. The defendants allegedly imported medical devices by means of false declarations regarding the description, value, or uses for the devices. The defendants then introduced medical devices for use in humans that were misbranded in that they were not approved nor cleared by the FDA. Further, they allegedly promoted the medical devices for unauthorized uses and concealed their conduct from internal investigators at Spectranetics and investigators from the FDA and DHS.

Spectranetics previously paid $5,000,000 in a civil and criminal matter related to this case. The company also is subject to an agreement with the government that requires the company's continued cooperation.

FDA NEWS

FDA may allow testing of drug cocktails for cancer

The FDA appears ready to allow innovative testing of drug cocktails to treat for cancer, according to Dr. Richard Pazdur, director of the FDA's Office of Oncology Drug Products in the Center for Drug Evaluation and Research (CDER). The combinations must meet three criteria: (1) there is a scientific rationale for how the drugs will work together in the body, (2) there is preclinical or Phase I data showing the combination is more than additive, and (3) there is a compelling reason why each drug cannot be successful independently.

FDA flags drugs for potential safety problems

In its quarterly drug safety list, these drugs were among those flagged by the FDA between April and June 2010 as having potential safety problems:

- AMAG Pharmaceuticals' Feraheme (ferumoxytol), for iron overload
- Merck's Implanon, a birth control pill
- Roche's Herceptin (trastuzumab), for breast cancer
- Roche/Genentech's Invirase, for HIV
- Sanofi-Aventis's Multaq (dronedarone), an anticoagulant
- Shire's Fosrenol (lanthanum carbonate), a phosphate binder
- Takeda's Uloric (febuxostat), for gout

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest

(items in red are new since last week)

Date	Topic	Committee/Event
September 2010		
September 7	**Forest/Cerexa's ceftaroline fosamil injection** for infection	FDA's Anti-Infective Drugs Advisory Committee
September 14	**Reauthorization of the medical device user fee program**	FDA public meeting
September 15	**Abbott's Meridia** (sibutramine), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
September 15	**Laboratory-developed test** (LDT) regulations	FDA extension for comments ends
September 16	**Alkermes' Vivitrol** (naltrexone ER) for opioid dependence	FDA's Psychopharmacologic Drugs Advisory Committee
September 16	**Arena Pharmaceuticals/Eisai's Lorqess** (lorcaserin), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
September 16	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
September 17	**Generic drug user fee program**	FDA public meeting
September 20	**Boehringer Ingelheim's Pradaxa** (dabigatran), an anticoagulant	FDA's Cardiovascular and Renal Drugs Advisory Committee
September 22	Meeting on the challenges in developing medical devices, biotech drugs, and other treatments for **neglected tropical diseases**	Public hearing
September 23-24	Meeting on scientific issues in clinical development of aerosolized **antimicrobials for cystic fibrosis**	FDA public workshop
September 24	**Hologic's Selenia Dimensions** digital mammography tomosynthesis system	FDA's Radiological Devices Advisory Committee
September 30	Meeting on clinical trials for the development of **pediatric cardiovascular devices**	FDA public workshop
October 2010		
October TBA	**Allergan's Botox** (onabotulinumtoxinA) for chronic migraine	PDUFA date
October 15	**Boehringer Ingelheim's Pradaxa** (dabigatran), an anticoagulant	PDUFA date
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 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	**GlaxoSmithKline/Valeant's ezogabine** for epilepsy	New FDA PDUFA date
December 2010		
December 7	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
December 9	**Human Genome Sciences/GSK's Benlysta** (belimumab) for lupus	PDUFA date
December 25	**Bristol-Myers Squibb's ipilimumab** for advanced melanoma	PDUFA date
Other future meetings		
January 31, 2011	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	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

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