Trends-in-Medicine

Quick Takes

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

SHORT TAKES

- **ABBOTT's Meridia (sibutramine) –** The FDA will hold an advisory committee meeting on the results of the SCOUT trial, a 10,742-patient, randomized, safety study which showed that Meridia increases cardiovascular events in high-risk people. Officials didn't give an exact date for the panel, just saying it will be "soon."
- **ALLERGAN's Latisse (topical bimatoprost) –** An unnamed company has applied for FDA approval (seeking Paragraph IV certification) to sell a generic version before Latisse's patent expires in September 2012.
- **BIOGEN IDEC/ORPHAN BIOVITRUM –** Clinical testing of their Factor VIII inhibitor for hemophilia will continue after a 16-patient Phase I trial showed promising results and good safety. The drug reportedly has a longer half-life than Baxter's Advate (antihemophilic factor).
- **CERNER –** President Trace Devanny left the company on July 16 after 16 years. Chairman/CEO Neal Patterson took over the duties of president as well.
- **CLINUVEL PHARMACEUTICALS' Scenesse (afamelanotide) –** The company reported that a 1-year, multinational, 91-patient trial showed Scenesse "provided relief for sufferers" of erythropoietic protoporphyria (EPP), a rare disease that makes them sensitive to light, significantly reducing the pain experienced by participants. Currently, ~10,000 people worldwide suffer from EPP.
- **GENZYME's alemtuzumab** has been granted Fast Track status by the FDA, which should help speed approval once the company submits it to the FDA.
- **HOLOGIC** is acquiring privately-held **Sentinelle Medical**, which makes magnetic resonance imaging (MRI) breast coils, tables, and visualization software.
- **HOLOGIC/KV PHARMACEUTICAL's Gestiva (hydroxyprogesterone caproate injection, 17P)** was resubmitted to the FDA to prevent pre-term birth in women who are pregnant with a single baby and have spontaneously delivered a single baby pre-term in the past.

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- **JOHNSON & JOHNSON** is buying **Micrus Endovascular**, which makes catheters and other minimally-invasive devices – e.g., intracranial stents and microcoils – used to treat stroke-related problems in the brain. Micrus will become part of J&J's Codman neurosciences group.
- **MERCK's Movectro (cladribine)** was approved in Russia, making it the first oral multiple sclerosis (MS) treatment.
- **Pharmaceutical Research Manufacturers Association (PhRMA)** has a new president/CEO John Castellani, former head of the Business Roundtable, where he headed policy initiatives such as civil-justice reform, fiscal policy, and trade expansion, regularly testifying before Congress. He replaces Billy Tauzin who stepped down in June 2010. Castellani was named one of the 100 most influential people in corporate governance in 2007 by ***Directorship*** magazine. Prior to the Business Roundtable, he was executive vice president of Tenneco; vice president of state, federal, and international government relations for TRW; vice president for resources and technology at the National Association of Manufacturers; and an environmental scientist and strategic planner for General Electric.
- **PROTALIX BIOTHERAPEUTICS' taliglucerase alfa –** The FDA delayed its decision on this potential Gaucher disease therapy by four months to February 25, 2011. It would compete with Genzyme's Cerezyme (imiglucerase) which is in short supply because of manufacturing problems.
- **SELVITA's SEL-103 –** The company said it will collaborate globally with **Orion Pharma** on a development and commercialization program for SEL-103 in the symptomatic treatment of Alzheimer's disease and other cognitive disorders. Selvita will be responsible for early research, and Orion will do the preclinical and clinical development as well as commercialization.

NEWS IN BRIEF

ACTELION's Tracleer (bosentan) – no exercise benefit in systemic sclerosis

In a study reported in the July issue of ***Arthritis & Rheumatism***, Tracleer, an endothelin receptor antagonist, failed to improve exercise capacity in patients with systemic sclerosis. Tracleer is already approved to treat pulmonary arterial hypertension in systemic sclerosis, but its ability to increase exercise capacity by halting the progression of interstitial lung disease had been unknown.

The study was a one-year, prospective, double-blind, 163-patient, randomized trial. At one year, there was an improvement in the primary endpoint – 6-minute walk test (6MWT) – but it was not statistically significant. Tracleer improved 6MWT by 12 meters vs. a 9-meter *deterioration* with placebo. The study had been powered to show a 45 meter difference between the drug and placebo.

Aromatase inhibitors – new guidelines encourage use

The American Society of Clinical Oncology (ASCO) published new guidelines for aromatase inhibitor (AI) use in the ***Journal of Clinical Oncology***, urging women with ER+ breast cancer to "use an aromatase inhibitor either alone or before or after using tamoxifen." The new guidelines also say women may use an AI for up to five years – even after five years of tamoxifen use.

Electronic Health Records – meaningful use defined

The federal government issued the final definition for Meaningful Use (MU), and from a first read of the 864-page document it appears they listened to the IT community. The rules are somewhat easier but still tough. Among the changes:

- The final regulation has a target of 40% e-prescribing instead of the initially proposed 70% in Stage 1.
- Under the interim standard's all-or-nothing approach, failing to meet a single MU requirement would have resulted in disqualifying e-prescribers from receiving any payment for electronic health records (EHRs) they deployed.
- The requirement to submit claims and eligibility transactions electronically was deferred to Stage 2 MU.
- There are now 10 fewer mandatory measures for eligible providers and hospitals in 2011-12. From the remaining 10 that are now optional, hospitals/providers can pick five, and a passing score is meeting 20 out of 25.
- Many measurements now have simplified denominators, often based on unique patients, not visits.
- Hospitals will qualify as meaningful users under Medicaid if they qualify under Medicare.
- Computerized physician order entry (CPOE) is now only required for medications in Stage 1, and the medication orders can be entered by licensed healthcare providers as well as physicians.

EXALENZ BIOSCIENCE's BreathID – additional trials needed

This device for diagnosing liver disease was rejected by the FDA, which wants additional pre-approval trials using pre-specified endpoints. The company said it will conduct the requested studies. BreathID is a point-of-care breath test platform capable of analyzing parts-per-million changes in carbon 13 and carbon 12 ratios in a patient's breath.

Hemopressin – a peptide that reduces food intake

U.K. researchers identified a short, nine-amino acid peptide in the rat brain that is an inverse agonist of the cannabinoid receptor that appears to decrease food intake. The research was published in the ***Journal of Neuroscience***. The peptide, hemopressin, specifically blocks the hyperphagic response to the cannabinoid receptor agonists but was found to have no effect on eating behavior in mice without the receptor. When administered centrally or systemically to rats and mice, hemopressin decreased nighttime food intake in a dose-dependent fashion with no obvious adverse effects. *Perhaps new diet drugs will result from this research.*

Infusion Pumps

- **BAXTER's Colleague Volumetric Infusion Pumps – FDA outlines recall details**

  After rejecting Baxter's latest plan for the recall of as many as 200,000 of its Colleague Volumetric Infusion Pumps that are currently in use in the U.S., the FDA told Baxter just how the recall will have to be handled. Baxter must:

  - Provide a **transition guide** for facilities using Colleague infusion pumps. The guide will include a list of FDA-cleared or approved pump alternatives, suggestions to help minimize disruption and patient risk during the transition period, and detailed information on the refund, replacement, and lease termination programs.
  - Provide customers with a **refund, a replacement pump, or a lease termination**.
  - Complete the recall and the replace/refund programs by **July 14, 2012**.

  Under the FDA mandate, Baxter will continue to provide batteries, spare parts, and service for the affected pumps during the transition period for customers who submit a Certificate of Medical Necessity to Baxter. The certificate, provided by Baxter, asks for information such as the number of Colleague pumps currently in use, serial numbers, and the anticipated date that the pump will be removed from use. After receiving the completed certificate, Baxter will continue service through mid-July 2012 or until the customer has transitioned to another pump, whichever comes first.

  How is the refund to be calculated? The FDA said, "The refund amount should provide healthcare facilities with adequate resources to make the best purchasing decisions for their facilities to replace the Baxter Colleague. The FDA understands that many facilities will have to buy pumps outside of their normal purchasing cycles, so FDA determined the refund to be 90% of the depreciated value of the purchase price of the pump, depreciated on a 10-year, straight-line monthly depreciation scale. The FDA stopped the depreciation of the pumps on June 29, 2006, the date of entry of the Consent Decree of permanent injunction. We did not order a full refund because healthcare facilities have received some fair use of the pumps while under the consent decree, and owners of pumps should not receive a refund that was greater than their purchase price."

- **HOSPIRA's Symbiq – Class I recall ordered**

  The FDA ordered a Class I recall of two Hospira infusion pumps – Symbiq One-Channel and Symbiq Two-Channel Infusers – because the devices may fail to detect air in line at the end of an infusion, which is potentially fatal for a patient, though the company has not had any reports of serious adverse events associated with these pumps.

Left ventricular assist devices (LVADs) – former Vice President Cheney got one

Cheney, who has a history of cardiac problems, got an LVAD recently, though it wasn't announced exactly which brand he got or whether it was bridge-to-transplant or as destination therapy. LVAD use may get a boost – and referrals may pick up – as the publicity surrounding the former VP raises awareness, provided all goes well for him. And that's the problem. If it doesn't go well, the publicity could backfire and hurt LVAD referrals and use.

LILLY and DAIICHI SANKYO – collaborating with Accumetrics

Lilly and Daiichi Sankyo will try to boost use of their anti-clotting drug, Effient (prasugrel), by urging doctors to use Accumetrics point-of-care VerifyNow platelet reactivity test more often on patients taking Sanofi-Aventis's Plavix (clopidogrel), hoping the Plavix patients will be non-responders, so doctors will switch them to Effient. The collaboration is also good for Accumetrics because use of VerifyNow needs a boost as well.

Magnetic resonance imaging (MRI) – beats CT for stroke diagnosis

New guidelines published in ***Neurology*** state that diffusion MRI scans should be used instead of CT scans to diagnose acute ischemic stroke within 12 hours of first symptoms. Guideline lead author Dr. Peter Schellinger of the Johannes Wesling Clinical Center in Germany said, "While CT scans are currently the standard test used to diagnose stroke, the Academy's guideline found that MRI scans are better at detecting ischemic stroke damage compared to CT scans." The guideline was based, in part, on a large study showing that stroke was accurately diagnosed with MRI.

Studies reviewed for the new guideline also showed that specific types of MRI scans more accurately identify the severity of stroke and more accurately diagnose lesions that

may be due to other medical conditions that produce symptoms similar to those of stroke. In addition, MRI scans also identify stroke lesions early, and the guideline gives clear direction that MRI should be used first in the emergency room setting. Schellinger said it was not clear, however, whether MRI should be used to detect stroke in clinical settings.

According to the new guideline, one situation in which CT may still be used first is when an IV thrombolytic is required but MRI is not immediately available. CT can be used in order to avoid a delay in administering the thrombolytic, and an MRI can be performed later if more information is needed.

MEDTRONIC's Sprint Fidelis ICD leads – can be successfully explanted

Sprint Fidelis leads were recalled in October 2007, but electrophysiologists were not urged to prophylactically replace the ones already implanted, just when a problem arises. But if the leads have to come out, a study in the June 30, 2010, issue of the ***Journal of the American College of Cardiology***, offered some reassuring news: it is safe and feasible to remove them.

Current guidelines cite a major complication rate of 1.4%-7.3% with extractions, but researchers from Brigham & Women's Hospital in Boston, did a retrospective cohort study of 348 consecutive patients undergoing extraction of Sprint Fidelis (models 6930, 6931, 6948, and 6949) leads at five high-volume centers, and they found:

- The average duration of the implanted lead was 27.5 months.
- 49.4% of leads were fractured.
- 26.5% were extracted prophylactically.
- 22.8% were extracted due to infection.
- Extraction was achieved with simple traction with 49.4% of leads, and CTS (counter traction sheath) assistance was required in 50.6% of cases.
- There were no major procedural complications or deaths.

However, the researchers are "not advocating that all Sprint Fidelis leads be extracted. The present study demonstrates that, in selected patients and in experienced hands, the current recommendations regarding Sprint Fidelis extraction warrant reconsideration."

MERCK/CARDIOME's Brinavess (vernakalant) – European approval recommendation

Brinavess has moved a step closer to approval in Europe, with a positive recommendation from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP). The proposed indication for Brinavess – an IV atrial-selective, potassium and sodium-channel-blocking agent – is for the rapid conversion of recent onset of atrial fibrillation (AFib) to sinus rhythm in adult non-surgery patients with AFib of ≤7 days and for post-cardiac surgery patients with AFib of ≤3 days. The FDA wanted additional information, and a trial to answer the Agency's questions is underway.

Orthopedic knee surgery – natural better than metal or plastic?

According to a report in ***Orthopedics this Week***, a study published in the U.K. in the ***Journal of Bone and Joint Surgery*** found that over the long term (up to 12 years), meniscus allograft transplants held up very well. All patients showed statistically significant improvements in pain and activity levels at two-, three-, five-, seven-, and 10-year time points vs. baseline. Furthermore, all but one of the improvements lasted up to 10 years. Further operations were necessary in ~19% of patients, and 6.7% needed revision surgery. But the results suggest that allograft transplants could be a first choice over artificial implants.

QUINCY BIOSCIENCE's apoaequorin – jellyfish protein improves cognition

A protein from the *Aequorea Victoria* jellyfish called apoaequorin appears to improve cognitive function and may be a potential treatment for Alzheimer's disease. In a randomized, placebo-controlled study of 35 adults (average age 61) with memory concerns, the calcium-binding protein improved cognitive testing scores by 14% vs. placebo after 60 days of treatment. The results were presented at the Alzheimer's Association International Conference in Honolulu.

SANOFI-AVENTIS's Arava (leflunomide) – gets boxed warning about risk of severe liver injury

FDA is adding information on severe liver injury to the Arava boxed warning. Liver injury is not a new risk factor with this rheumatoid arthritis drug. The FDA previously required a Boxed Warning stating that Arava was contraindicated in pregnant women or women of childbearing potential who were not using reliable contraception. The FDA said the decision to add the information about severe liver injury to the Boxed Warning was based on 49 reports of severe liver injury, including 14 cases of fatal liver failure, between 2002 and 2009. In the FDA review, the greatest risk for liver injury was seen in patients taking other drugs known to cause liver injury and in patients with pre-existing liver disease.

Now, the FDA is recommending that:

- Patients with pre-existing liver disease not receive leflunomide.
- Patients with elevated liver enzymes (ALT >2xULN) not receive Arava.
- Use caution in patients who are taking other drugs that can cause liver injury.

- Monitor liver enzymes at least monthly for three months after starting Arava and at least quarterly thereafter.
- If ALT rises to >2xULN on Arava, the drug should be stopped, cholestryamine washout begun to speed the removal of Arava from the body, and follow-up liver function tests conducted at least weekly until the ALT value is within the normal range.

SANQUIN's Nonafact (human coagulation Factor IX concentrate) – stops surgical bleeding

The purified, monoclonal antibody concentrate of plasma-derived Factor IX appears to stop both spontaneous and surgical bleeding in patients with hemophilia, according to a pooled analysis of four studies presented during the Hemophilia World Congress 2010. In 12 patients, Nonafact was administered to patients undergoing surgery, and clinical response was rated as "excellent" in 92%. Nonafact was not associated with thromboembolic events or abnormal laboratory values, and no development of Factor IX inhibitors were observed.

Scientists' instincts – may *not* lead to good drug discovery decisions

A study by Optibrium, a company that offers software solutions for drug discovery, and Tessella, an information technology and consulting services company, suggests the answer is No. In the study, which was published in ***Drug Discovery Today***, the authors said the challenges to scientists' decision making arise from the:

- Importance of multiple/conflicting criteria to the success of a potential drug molecule.
- Large amount of data generated.
- Inherent uncertainty in the data.

Biased decisions can lead scientists to miss good compounds by not searching widely enough, by wasting resources, and by clinging to ideas that should be dismissed, the authors found. *So, how can scientists make better individual and team decisions about drug discovery?* The study suggests:

- More feedback on problem solving performance.
- More use of computational tools.

The authors noted that there are trends to more technology investment, outsourcing of shared services, and formation of smaller, disease-specific units (which bring researchers closer to clinicians), but they warned that senior management cannot afford to ignore the human dimension.

FDA NEWS

Angiotensin receptor blockers (ARBs) – is there a cancer risk?

The FDA has begun a safety review of ARBs after a meta-analysis suggested that ARBs may be associated with a small increased risk of cancer. The meta-analysis included data from >1,000 patients in several long-term, randomized ARB safety trials, with a mean duration of follow-up of 1.7-4.8 years, found the frequency of new cancers was 7.2% for ARB patients vs. 6.0% for those not receiving ARBs (risk ratio = 1.08). No statistically significant difference in cancer deaths was reported.

FDA device approval process criticized

Public Citizen released a study which found that the FDA's system for approving medical devices "is broken, allowing potentially ineffective devices on the market largely because approval rules are too lax, contain loopholes, and are inadequately enforced."

The study outlines eight weaknesses in the device approval process. Among these are:

- A lower approval standard for devices than for drugs.
- "Lax interpretation" of the requirements for 510(k) clearance.
- A "loophole" that allows manufacturers of novel devices to "circumvent the PMA pathway."
- Failure of the FDA to "appropriately regulate many types of devices that were first marketed prior to the 1976 enactment" of the current FDA regulatory review programs.
- A "superfluous appeal mechanism" that gives manufacturers a "second go" for approval after the FDA rejects a device.
- Allowing companies to use the "least burdensome" means of showing a device's effectiveness.
- Allowing manufacturers to challenge many FDA requests they consider onerous.

Among the devices that Public Citizen cited as having problematic approvals:

- **Cyberonics**' VNS, a vagus nerve stimulator to treat severe depression.
- **ReGen**'s Menaflex, a collagen meniscus implant for the knee.

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

Date	Topic	Committee
Date TBA	**Abbott's Meridia** (sibutramine), a diet drug	Endocrinologic and Metabolic Drugs Advisory Committee to review the SCOUT trial data
	July 2010	
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	**Medtronic's Amplify rhBMP-2 Matrix**	Orthopedic and Rehabilitation Devices Panel of the Medical Devices 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 19	**Lilly's Cymbalta** (duloxetine) for chronic pain	Anesthetic and Life Support 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 7	**Forest/Cerexa's ceftaroline fosamil injection** for infection	Anti-Infective Drugs Advisory Committee
September 16	**Arena Pharmaceuticals/Eisai's lorcaserin**, a diet drug	Endocrinologic and Metabolic Drugs Advisory Committee
September 17 (not confirmed)	**Boehringer Ingelheim's Pradaxa** (dabigatran)	Cardiovascular and Renal Drugs Advisory Committee

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