TRENDS-in-MEDICINE

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by Lynne Peterson

Quick Takes

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

Trends-in-Medicine
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SHORT TAKES

- **ALDAGEN's ALD-401 –** The FDA has given the go-ahead for an ~100-patient Phase II trial of this regenerative cell therapy for stroke patients. Participants will receive an injection of ALD-401 stem cells 13-19 days after suffering a stroke. The trial will test the ability of the stem cell therapy to alleviate stroke damage.

- **ANGIOSCORE's AngioSculpt PTA**, a scoring balloon catheter, is being recalled worldwide after "a small number" of reports that the device's bond has the potential to fail, which could lead to arterial injury, though no injuries have yet been reported.

- **ANTIGENICS** changed its name to **Agenus**.

- **BIPAR SCIENCES' iniparib (BSI-201) –** A study by researchers at Baylor Sammons Cancer Center that was published in the ***New England Journal of Medicine*** found that adding this PARP inhibitor to standard chemotherapy (gemcitabine and carboplatin) increased survival in women with triple negative breast cancer (12.3 months vs. 7.7 months with chemotherapy alone).

- **BOSTON SCIENTIFIC** is buying **Intelect Medical**, a company that makes brain stimulation technology, for $60 million in cash. Intelect Medical has been developing a programming system to permit doctors to visualize which parts of the brain to best target for stimulation. Boston Scientific reportedly plans to pair that technology with its own Vercise deep-brain stimulation system, which is undergoing clinical trials for the treatment of Parkinson's disease.

- **BRISTOL-MYERS SQUIBB's Yervoy (ipilimumab) –** First, the FDA postponed the Oncologic Drugs Advisory Committee (ODAC) meeting from December 2, 2010, to February 9, 2011, on this treatment for advanced melanoma. Now, the FDA has cancelled the February meeting, saying "the issues for which the FDA was seeking the scientific input of the committee have been resolved." The PDUFA date is March 26, 2011.

- **CUMBERLAND PHARMACEUTICALS' ACETADOTE (injectable acetylcysteine) –** Six lots of this drug, which is used to prevent acute liver injury in patients taking potentially toxic amounts of acetaminophen, were recalled due to particulate matter found in some 30 mL glass vials. The company said no adverse events have been reported, calling the recall "precautionary." The particulates apparently were introduced by the glass vial supplier, which is now a former supplier.

- **CVS CAREMARK** is buying the Medicare Part D unit of **Universal American Financial Corp.**, which will allow CVS to expand its pharmacy-benefit management business.

- **EUROMEDIC INTERNATIONAL** reportedly will sell its kidney dialysis unit to **Fresenius Medical Care AG**. If regulators approve the deal, Fresenius will be able to operate dialysis clinics within Russia and Eastern Europe.

- **INVACARE** received a warning letter from the FDA alleging that the company failed to adequately investigate reports of entrapment and fires associated with its electric beds.

- **JOHNSON & JOHNSON/BAYER's Xarelto (rivaroxaban)** was filed with both European regulators and the FDA for stroke prevention in patients with atrial fibrillation. Xarelto already is approved in Europe for the prevention of thrombosis after orthopedic surgery, but in May 2009 the FDA rejected that indication, asking for more information, and J&J has now responded to that request.

- **JUVENTAS THERAPEUTICS' JVS-100** – The FDA has authorized the company to begin a Phase II trial of JVS-100 for the treatment of critical limb ischemia.

- **LIGAND PHARMACEUTICALS** licensed two liver disease drugs – pradefovir for hepatitis B and MB-01733 for hepatocellular carcinoma – to **Chiva Pharmaceuticals**, giving Chiva development and marketing rights in China.

- **MERCK** plans to "refocus" its research spending and will make "tough" decisions about resources, halting development of less promising drugs much quicker.

- **MERCK's boceprevir** – Both U.S. and European regulators have granted expedited review to this antiviral therapy for hepatitis C.

- **MERCK's Implanon, a contraceptive implant** – The U.K.'s Medicines and Healthcare Products Regulatory Agency has received more than 1,500 complaints of side effects – including pain and scarring – linked to Implanon since 1999, and 584 women said they had unplanned pregnancies while on the contraceptive. Merck claims the failure rate "isn't exceptional."

- **OPEXA THERAPEUTICS' Tovaxin**, an autologous T-cell vaccine for multiple sclerosis, was given the green light by the FDA to begin a Phase III trial. The FDA also agreed that the company's new manufacturing process for the personalized vaccine is acceptable for use in a pivotal trial, but the company plans to submit additional information on chemistry, manufacturing, and control process before starting the study. Opexa continues to look for a partner.

- **OPTIMER PHARMACEUTICALS' fidaxomicin**, which was submitted to the FDA in December 2010 for the treatment of pediatric *Clostridium difficile* (*C. diff*), was granted orphan drug status.

- **PFIZER and SANTARIS PHARMA** expanded their partnership on RNA drugs.

- **PFIZER's Chantix (varenicline)** – Pfizer underestimated the demand for its smoking cessation drug in Japan (where it is sold as Champix) and actually ran out of supply. The Japanese government increased the tax on cigarettes on October 1, 2010, which apparently spurred more people than expected to quit smoking, and by mid-October, Pfizer had to suspend Champix sales to new patients until it could ramp up production.

- **PROSTRAKAN's Abstral (fentanyl transmucosal tablets)**, a Schedule II opioid, was approved by the FDA for breakthrough cancer pain. The FDA also mandated a strict Risk Evaluation and Mitigation Strategy (REMS) that the Agency plans as the model for all transmucosal fentanyls. Under the REMS, pharmacies, distributors, and healthcare professionals who prescribe to outpatients must be enrolled in order to prescribe, dispense, or distribute Abstral. FDA directed other sponsors in this class of drugs to work together on a single shared system to implement the REMS.

- **RANBAXY and MERCK** ended their drug discovery collaboration to develop new antibacterial and antifungal drugs.

- **RITEDOSE's 0.083% albuterol sulfate inhalation solution**, which is used to treat asthma, was withdrawn from the U.S. market because the product's label had incorrect concentration data, which could lead to overdose and cause possibly fatal side effects.

- **ROCHE/GENENTECH's Avastin (bevacizumab)** – Now that the FDA has started the process to remove the breast cancer indication for Avastin, some local Medicare carriers – including Palmetto – plan to stop paying for any new breast cancer patients to start therapy with the drug.

- **SPECTRUM PHARMACEUTICALS** plans to develop a biosimilar version of Roche's Rituxan (rituximab) through a new partnership with **Viropro**.

- **XOMA's XOMA-052** – Xoma licensed XOMA-052, an anti-inflammatory (anti-IL-1) drug, to **Les Laboratoires Servier**, but Xoma retained development and sales rights for Behcet's uveitis and other inflammatory and cancer indications in the U.S. and Japan.

NEWS IN BRIEF

Amyotrophic lateral sclerosis (ALS) – due to a retrovirus?

Researchers at Johns Hopkins University reported – in a paper published in the ***Annals of Neurology*** – results that suggest that retroviral genes and proteins could be a useful biomarker for ALS. They examined the brains of 28 ALS patients, 12 chronic disease (coronary and cancer) patients, 10 accidental death patients, and 12 Parkinson's disease patients. They found the retrovirus HERV-K was active to varying degrees in almost all the ALS and chronic disease patients. The question is whether the HERV-K is causative or just associative. And other retroviruses could be active as well. But if ALS is due to a retrovirus, perhaps some of the antiretroviral drugs that pharmas have in their library could be tested against ALS.

DARA BIOSCIENCES' DB-959Na – info trickling out

The company previously announced that this oral PPAR (peroxisome proliferator activated receptor) delta/gamma agonist for Type 2 diabetes had safety comparable to placebo, controlled glucose, raised HDL, and lowered triglycerides. Now, the company released information from a randomized, Phase I study in 76 healthy volunteers which found that the maximum tolerated single oral dose is 200 mg QD, which is "well beyond" the anticipated therapeutic dose. In 1H11 the company plans to both present detailed results at a medical conference and initiate a multiple ascending dose trial.

FOREST LABORATORIES and ALMIRALL's inhaled aclidinium bromide – positive Phase III results

The results of the 6-month, 828-patient, placebo-controlled Phase III ATTAIN study found the 200 µg and 400 µg doses (administered BID in a multidose dry powder inhaler) met the primary endpoint and key secondary endpoints in moderate-to-severe COPD. In the study, aclidinium significantly improved FEV1 overall, peak FEV1, the percent of patients with a meaningful reduction in breathlessness, and the percent of patients with improved respiratory health status. The companies now plan to file for U.S. and European approval by mid-2011.

Glaucoma – new findings about vision loss

A study funded mostly by the Glaucoma Research Foundation and published in the ***Proceedings of the National Academy of Sciences*** made three discoveries:

1. **New similarities to Parkinson's disease –** Glaucoma is characterized by formation of protein aggregates (gamma-synuclein). In Parkinson's disease, a very similar protein (alpha-synuclein) is aggregated. The researchers said this finding provides evidence that glaucoma acts more like protein aggregation neurodegenerative diseases than like other eye diseases that cause blindness.
2. **New cellular mechanism –** Astrocytes were discovered to have a highly unexpected role in cleaning up the by-products of the retinal ganglion cells that die in glaucoma. This may help explain perplexing findings in many neurodegenerative disorders besides glaucoma.
3. **Underlying cause of vision loss –** It has been known that vision loss in glaucoma most likely occurs on the optic nerve head, but now researchers have found where within the optic nerve head the blinding insult is likely to be, which would explain the very characteristic pattern of blindness in glaucoma.

The researchers are optimistic that these findings may lead to new treatments for glaucoma and help in research of other neurodegenerative diseases.

Implantable cardioverter defibrillators (ICDs) – huge off-label use

A registry study published in the ***Journal of the American Medical Association*** found that 23% of ICDs implanted for primary prevention (or 18% of all ICD implants) did not meet the guidelines for use. In addition, patients who got ICDs for off-label purposes had higher rates of in-hospital death and complications vs. on-label patients. The off-label use was often related to timing – patients getting an ICD sooner than guidelines call for:

- Within 40 days of an MI.
- Post-CABG.
- Newly diagnosed heart failure patients.
- Patients with severe heart failure.

The question is whether this study will spur Medicare and other payors to limit coverage to on-label patients.

India
– may limit foreign pharma investment

Indian regulators are considering a 49% limit on foreign direct investment in Indian pharmaceutical companies and a requirement that the investments be approved by the Indian government. The new rules are being discussed because of concerns that increasing foreign buyouts of Indian drugmakers is hurting the affordability of medications.

NOVABAY PHARMACEUTICALS' NVC-422
– early positive results against superbugs

The company announced that tests conducted at a third-party laboratory showed that its Aganocide anti-infective has *in vitro* activity against the superbug NDM-1 (New Delhi Metallo-beta-lactamase-1) as well as six other highly drug-resistant pathogens: *Enterococcus faecium, Staphylococcus aureus, Klebsiella species, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter*. Additional data are expected to be presented at the 2011 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC).

TEVA

- **Metronidazole –** The company recalled 75 bottles of this antibacterial due to some tablets being underweight. So far, 50 bottles have been returned to the company.
- **ProAir HFA asthma inhalers –** The company recalled nearly 800,000 of these devices because they failed tests to ensure they had identical contents. Three of four lots involved have already expired, and the other expires this month.

REGULATORY NEWS

FDA launches website to answer industry questions
– goal is transparency

The FDA announced it is launching a website (FDA Basics for Industry) that will explain its regulations to companies as part of its transparency effort. The website will have answers to frequently asked questions about the regulation of food, drugs, and medical devices. FDA officials also said they will make every effort to respond to questions from manufacturers within five business days.

FDA leadership change – transitions trigger review

Dr. Joshua Sharfstein is leaving his post as principal deputy FDA commissioner to become Maryland's Secretary of Health and Mental Hygiene.

In announcing Dr. Sharfstein's departure (and other FDA personnel changes), FDA Commissioner Dr. Margaret Hamburg said she will be using the next two months for an internal FDA review: "In light of these many transitions, I would like to take this opportunity to consult with senior FDA leaders and review certain functions and positions. My top priority is advancing FDA's public health mission."

During Dr. Hamburg's "review" of the Agency, John Taylor, currently Counselor to the FDA Commissioner, will serve as the Acting Principal Deputy FDA Commissioner.

U.K.'s National Institute on Clinical Excellence (NICE) – considering coverage of Avastin for AMD

Roche/Genentech did not ask NICE to approve coverage of Avastin (bevacizumab) for wet age-related macular degeneration (AMD) and, in fact, opposes the idea, but NICE is reviewing Avastin for AMD anyway.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	January 2011	
January 12	**Alnara Pharmaceuticals' Solpura** (liprotamase capsules) for exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, etc.	FDA's Gastrointestinal Drugs Advisory Committee
January 19	**Erythropoiesis stimulating agents (ESAs)** for anemia in adults with CKD	CMS Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)
January 20	**Avid Radiopharmaceuticals' florbetapir F-18 injection** for β-amyloid measurement in Alzheimer's disease	FDA's Peripheral and Central Nervous System Drugs Advisory Committee
January 21	**Bayer's gadobutrol injection**, an MRI contrast agent for brain and CNS imaging	FDA's Peripheral and Central Nervous System Drugs Advisory Committee
January 25	Consideration of reclassification of **automated external defibrillators** from PMA to 510(k) products	FDA's Circulatory System Devices Advisory Committee
January 26	**Abbott's RX Acculink** carotid stent system	FDA's Circulatory System Devices Advisory Committee
January 26 (approx.)	**Mannkind's Afrezza** (inhaled insulin)	PDUFA date
January 27-28	Discussion of **possible reclassification of electroconvulsive therapy devices**	FDA's Neurological Devices Advisory Committee
January 31	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	PDUFA date
	February 2011	
February 8	Review of **postmarketing studies for cancer drugs** receiving accelerated approval prior to January 1, 2009	FDA's Oncologic Drugs Advisory Committee (ODAC)
February 9 (cancelled)	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for the treatment of advanced melanoma in patients who have received prior therapy	FDA's Oncologic Drugs Advisory Committee (ODAC)
February 9	Public workshop on expanding ***in vivo* biomarker detection devices**, focusing on research opportunities and technical challenges	FDA and the Defense Advanced Research Projects Agency (DARPA)
	Other future 2011 meetings	
March 5 (approx.)	**Merck KGaA's cladribine** for multiple sclerosis	PDUFA date
March 7	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
March 8	**Novartis's Arcapta Neohaler** (indacaterol maleate), a QD bronchodilator for long-term use in COPD	FDA's Pulmonary-Allergy Drugs Advisory Committee
March 10	Risk of **neurodegeneration in pediatric patients** from anesthetic drugs	FDA's Anesthetic and Life Support Drugs Advisory Committee
March 10	**Human Genome Sciences/GSK's Benlysta** (belimumab) for lupus	PDUFA date
March 26	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for advanced melanoma	PDUFA date
April 10	Open forum to discuss statistical issues related to **drug and biologics development and review**	Joint FDA and Drug Information Agency Forum
June	**King Pharmaceuticals/Pain Therapeutics' Remoxy** (tamper-resistant oxycodone CR) for pain	Approximate PDUFA date
Summer	Report on **FDA 510(k) reform**	Institute of Medicine
October 20	**Johnson & Johnson's abiraterone** for metastatic prostate cancer	PDUFA date