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

- **ADVANCED CELL TECHNOLOGY** submitted an application to the European Medicines Agency (EMA) seeking orphan drug status for its retinal pigment epithelial cell-based embryonic stem cell treatment for patients with Stargardt's disease.
- **ARROW's Ultra 8 intra-aortic balloon catheters (IABS)** – The FDA announced several of these catheters were recalled because they can become stuck in the sheath. When that happens, the user is unable to move the IAB catheter forward or backward, causing delay in therapy, bleeding, or arterial injury.
- **CEPHALON's Nuvigil (armodafinil)** – For the second time, the FDA failed to approve Nuvigil as a treatment for jet lag, instead issuing another complete response letter expressing concerns about the "robustness" of the clinical data on that indication. The issue appears to be the risk:benefit balance; Nuvigil is associated with rare but life-threatening cases of Stevens-Johnson syndrome (a serious skin rash). As a result, Cephalon said it is giving up on that indication.
- **Compounded drugs** – A coalition of corporations, insurance companies, and labor unions is pushing for legislation in California that would put restrictions on compounded drugs, claiming the prescribing of these drugs is being abused, particularly in the workers' comp area. The proposed legislation would limit the price of medically necessary compounded drugs by adding them to the state's fee schedule.
- **COVIDIEN/EV3's NanoCross .014" OTW PTA dilatation catheter** was pulled from the market because the device's shaft has the potential to break during a procedure, possibly leading to unplanned surgery, injury, or even death.
- **GILEAD's ambrisentan** – The company stopped a Phase III trial of this endothelin receptor antagonist to treat idiopathic pulmonary fibrosis (IPF) because the drug failed to help patients any more than placebo. However, last week Gilead announced it was buying **Arresto Biosciences**, which has an antibody in development for IPF, AB-0024.
- **HEARTWARE's HeartWare** – The company submitted a PMA to the FDA for this ventricular assist system as a bridge to heart transplantation for patients with end-stage heart failure.
- **KING PHARMACEUTICALS/PAIN THERAPEUTICS' Remoxy (tamper-resistant oxycodone CR)** was resubmitted to the FDA for moderate-to-severe pain. The opioid was rejected by the FDA in December 2008. The PDUFA date is June 2011.
- **MARINA BIOTECH's CEQ-508**, a drug in development to treat familial adenomatous polyposis, was granted orphan drug status by the FDA.

- **MEDTRONIC's Hydrosorb Mesh** – Two prominent senators, Sen. Max Baucus (D-MT) and Sen. Chuck Grassley (R-IA), are investigating whether this orthopedic device, which contains the company's bone morphogenic protein product, Infuse, was used off-label in a trial in patients at Walter Reed Army Medical Center without the consent of the patients.
- **OMEROS' OMS-201**, an anti-inflammatory agent and smooth muscle relaxant, was "well tolerated" and showed good clinical results in a Phase I/II study in patients undergoing ureteroscopies for removal of ureteral or renal stones.
- **PROMETHEUS LABORATORIES' PRO-PredictRx**, a test to determine proper thiopurine doses, is eligible for patent protection, the U.S. Court of Appeals for the Federal Circuit ruled.
- **SANTARUS' Rhucin (recombinant human C1 esterase inhibitor)**, which was licensed from **Pharming Group**, was submitted to the FDA for the treatment of hereditary angioedema.
- **SXC HEALTH SOLUTIONS**, a pharmacy benefits manager, has completed its buyout of specialty pharmacy provider **MedfusionRx**, which provides clinical services to patients with complex clinical conditions, including cancer, multiple sclerosis, and hepatitis.
- **TEVA's Copaxone (glatiramer acetate)** – The bad news for Teva is that the FDA rejected a lower-volume form of this injectable multiple sclerosis drug, saying the mechanism of action of Copaxone is not fully understood, so even a formulation change could affect clinical outcomes. The good news is that this decision is likely to make it tougher for generic Copaxone to get approved.

NEWS IN BRIEF

AMERICAN REGENT – two recalls

1. Dexamethasone sodium phosphate injection – The 4 mg/mL and 30 mL multiple-dose vials were recalled because some vials were found to contain particulates or have the potential to form particulates prior to their expiration date. Hospitals, infusion centers, and other healthcare facilities were warned not to use the product with the affected lot numbers and to return any recalled items to the company.

2. Sodium bicarbonate injection – The 7.5% and 8.4% 50 mL single-dose vials – which are used to treat metabolic acidosis, certain drug intoxications, or severe diarrhea – were recalled because some lots contain particulates. Potential adverse events after IV administration include damage to blood vessels in the lung, localized swelling, and granuloma formation.

BIOLINERX's BL-5010 – positive Phase I/II results

An open-label, single-arm, 60-patient, Phase I/II trial conducted in Germany and the Netherlands found this novel non-surgical therapy was safe and effective for the removal of seborrheic keratoses. BL-5010 also preserved the lesions for later histological examination. In 96.7% of patients, the lesions sloughed off within 30 days of a single application of BL-5010.

Cardiac drugs – underused by patients

- **Warfarin** – A Medicare database study published in the journal ***Stroke*** found warfarin is used by only ~50% of elderly patients with atrial fibrillation (AFib) who should be taking it to prevent stroke. The study also found that AFib patients who take warfarin have more doctor visits but fewer hospitalizations.
- **SANOFI-AVENTIS's Plavix (clopidogrel)** – A Brazilian study looking at Plavix discontinuation rates found that 66 of 400 consecutive patients discontinued use of Plavix within a month of starting it, and the No. 1 reason was cost. Interestingly, 15% of patients quit because another physician advised them to stop.

IMMUNE NETWORK's V5 immunomodulator – early results positive

Positive results from the first half of a 120-patient trial (IMM-01) in patients with re-treated, multidrug-resistant, or HIV-coinfected tuberculosis were published in the journal ***Immunotherapy***. The study, which was conducted in the eastern Ukraine, confirmed the results of an open-label trial published in October 2010 in the ***Journal of Vaccines and Vaccination.*** The current study found V5 was safe and was not associated with any TB reactivation. Concurrent administration of V5 with either first- or second-line TB drugs resulted in clearance of *M. tuberculosis* in sputum smears of 96.3% patients vs. 25% of placebo patients. Sputum conversion occurred very quickly (within one month). V5 reversed TB-associated wasting, with average weight gain of 3.4 kg in 100% of V5 patients vs. 1.07 kg in 67.9% of placebo patients. V5 also eliminated TB-associated fever in 100% of patients vs. 39.3% of placebo patients.

MANNKIND's Afrezza (inhaled insulin, formerly called Technosphere) – delayed again

The FDA has delayed once again – this time for 4 more weeks – its decision on Afrezza, which was first submitted to the FDA in March 2009. Remember, Pfizer's inhaled insulin, Exubera, failed to gain much traction in the market either in Europe or in the U.S., and Pfizer pulled it from the market in 2007, partly for safety reasons. Mannkind also is being sued by a former regulatory affairs official who claims the company withheld information from the FDA about possible "scientific misconduct" at clinical trial sites in Russia and Bulgaria.

Nerve growth factor (NGF-1) inhibitors – is the class dead?

- **Regeneron Pharmaceuticals/Sanofi-Aventis's REGN-475/SAR-164877** has gone the way of **Pfizer's tanezumab**: Clinical trials halted in osteoarthritis by the FDA over concerns about avascular necrosis leading to joint replacement surgery. Apparently, a new case has popped up, but whether that was in a Pfizer study or another competitor's NGF program is unclear. Regeneron indicated the FDA now suspects this side effect is a class effect, dooming all NGFs. While Pfizer hasn't halted the pain trials with tanezumab, it now seems unlikely that the FDA would allow use in pain but not osteoarthritis.
- **Johnson & Johnson/Amgen's fulranumab**, which was being studied in pain, also was put on hold by the FDA, but J&J didn't announce the action because it is "not a material event for us." J&J said it doesn't know how many side effects have occurred with fulranumab, which seems unlikely since the company must notify the FDA about all serious adverse events.
- **AstraZeneca's MEDI-578** – Early-stage research was voluntarily suspended, even though no cases of avascular necrosis have been seen so far with this NGF inhibitor, while the company conducts an internal assessment.
- **Abbott/PanGenetics' ABT-110** appears to be the only NGF-1 antibody still "proceeding as planned."

REPROS THERAPEUTICS' Androxal (clomiphene) – positive news

The company said a single assessment of testosterone levels collected in the morning correlates to maximum and average levels of testosterone during a 24-hour period in patients taking oral Androxal. This is the measurement method the FDA said in November 2010 it prefers. Repros is trying to prove that its product – in contrast to topical testosterone products – maintains normal daily testosterone levels, with morning peaks and evening troughs.

REGULATORY NEWS

CMS creates new office for dual eligibles

The Centers for Medicare and Medicaid Services (CMS) has created a new office – the Federal Coordinated Health Care Office – to coordinate care for individuals who are simultaneously enrolled in the Medicare and Medicaid programs (known as dual eligibles). The office will be tasked with improving the overall quality of healthcare and long-term services for these beneficiaries.

FDA delayed guidance for digital pharma marketing

The FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC), which has been researching draft guidance on issues related to internet/social-media promotion of FDA-regulated medical products, has postponed release of any of its results until 1Q11. The Agency only promises that at least one of the following issues being considered will be addressed at that time:

- Responding to unsolicited requests.
- Fulfilling regulatory requirements when using tools associated with space limitations.
- Fulfilling postmarketing submission requirements.
- Online communications for which manufacturers, packers, or distributors are accountable.
- Use of links on the internet.
- Correcting misinformation.

The FDA held two days of public hearings in November 2009, and industry had expected the draft guidelines to be issued by the end of 2010.

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 7	**Endo Pharmaceuticals' Opana TRF** (oxymorphone ER) for pain	PDUFA date
January 7	**AstraZeneca's vandetanib** for thyroid cancer	PDUFA date
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)	**New** 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 9	**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 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 2011	**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
Date TBA	Review of accelerated drug approval process	FDA's Oncologic Drugs Advisory Committee (ODAC)