Trends-in-Medicine

Quick Takes

by Lynne Peterson

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Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

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

SHORT TAKES

- **American access to European drugs –** A Pacific Research Institute report claims that American patients would benefit if the FDA "didn't have a monopoly on regulations." Instead, Americans should have access to medicines already approved in Europe, which would "increase regulatory competition, enable more patient choice, and potentially save the lives of those suffering life-threatening illnesses and who currently have no treatment options."
- **ANTARES PHARMA's Anturol gel** met the efficacy endpoint of reducing episodes of urinary incontinence in a 600-patient, randomized, 12-week, Phase III trial for overactive bladder. The study was testing two doses: 84 mg and 56 mg vs. placebo. A long-term safety study is ongoing and expected to finish in 4Q10. Antares hopes to file Anturol gel with the FDA by the end of 2010.
- **ANTIGENICS' AG-707 herpes simplex 2 vaccine –** The company reported positive results from a small (35-patient) early-stage trial of this therapeutic vaccine, with all 7 evaluable patients showing a significant CD4+ T-cell response to the virus.
- **ASTRAZENECA's Brilinta (ticagrelor) –** The FDA's Cardiovascular and Renal Drugs Advisory Committee voted 7-1 that Brilinta should be approved for the reduction of thrombotic events in patients with non ST-elevation and ST-elevation acute coronary syndrome (ACS) intended to be managed medically or by percutaneous coronary intervention (PCI). However, the panel did not think the drug should be labeled that it reduces stent thrombosis. The PDUFA date is September 16, 2010.
- **Centers for Medicare & Medicaid Services (CMS)** approved a two-year study that will evaluate the impact of genetic information and adverse events on individual patient responsiveness to warfarin. The >7,000-patient U.S. study, which will be conducted by Iverson Genetic Diagnostics, will assess adverse events,

including major bleeding complications, in patients administered warfarin and where genetic information (CYP2C9 and VKORC1 alleles) was used to individualize dose.

- **CEPHALON** asked the FDA to withdraw its approval of Watson Pharmaceuticals' generic Fentora (fentanyl buccal). Cephalon claims that Watson's generic Fentora is chemically different from Cephalon's Fentora and that Watson should be required to undertake a lengthier approval process.

- **CUBIST PHARMACEUTICALS' Cubicin (daptomycin) –** The FDA issued a drug safety communication warning healthcare professionals and patients of the potential for eosinophilic pneumonia with Cubicin, an IV antibacterial drug used to treat serious skin infections and bloodstream infections. Eosinophilic pneumonia is a rare but serious condition that can lead to respiratory failure and even death. Seven post-approval cases of likely Cubicin-related eosinophilic pneumonia were reported to the FDA's Adverse Event Reporting System (AERS) between 2004 and 2010. The drug's label has also been updated to include this information. Doctors are being advised to closely monitor patients treated with Cubicin for eosinophilic pneumonia.

- **Glucose control –** According to a study in the ***Clinical Journal of the American Society of Nephrology***, aggressive blood sugar control does ***not*** improve survival in diabetic patients with kidney failure, suggesting that physicians should individualize blood sugar targets for these patients. Researchers at Joslin Diabetes Center studied 24,875 dialysis patients for up to 3 years, and they found that only extremely high or extremely low blood sugar increased patients' risk of dying prematurely. In particular, patients with HbA_{1c} >11 were especially at risk, with a 21% increased likelihood of dying during the study. In the small subgroup of patients with Type 1 diabetes, those with HbA_{1c} >9 had a 52% increased risk of death during the study.

- **HOLOGIC's Selenia Dimensions** digital mammography tomosynthesis system will be reviewed by the FDA's Radiological Devices Advisory Committee on September 24, 2010. The system is intended for use in the same clinical applications as traditional mammographic systems.

- **HOSPIRA** plans to start a trial of a biosimilar to Amgen's Epogen (epoetin alfa). The FDA gave Hospira permission to begin the trial at 20 U.S. dialysis centers.

- **INGENIX (a UnitedHealth Group subsidiary) –** This healthcare IT and services company is acquiring Picis, a provider of healthcare IT for hospital emergency rooms and surgery and intensive care departments as well as hospital financial information systems.

- **MEDTRONIC's Amplify (rhBMP-2) –** The FDA's Orthopaedic and Rehabilitation Devices Advisory Committee voted 9-4-1 (yes, no, abstain) that the product is safe and 10-3-1 that it is effective, but they split 6-5-3 on the key question: Do the benefits outweigh the risks? Thus, the ball is really solely in the FDA's court.

- **MERCK KGaA's cladribine –** The FDA, which initially rejected this oral multiple sclerosis (MS) drug application as incomplete, has now granted it priority review, with a decision expected by the end of 2010. Russia approved cladribine for MS on July 12, but the company doesn't expect to start selling it there until early 2011. European regulators are expected to make a decision in 3Q10.

- **PFIZER's Selzentry (maraviroc) + Reyataz (atazanavir) –** A pilot study reported at the International AIDS Conference in Vienna, Austria, found that once-daily dosing of these two drugs – a cell entry inhibitor boosted with a protease inhibitor – was sufficient to suppress HIV in treatment-naïve patients, suppressing the virus to undetectable levels in 80% of patients with a viral load of 100,000 copies/ml. A Phase III study is planned.

- **SANOFI-AVENTIS** is trying to buy **Genzyme**.

- **SANOFI PASTEUR** – The FDA cited manufacturing deficiencies at the company's vaccine plant in France. FDA inspectors found Sanofi did not meet good manufacturing standards to prevent microbial contamination in the production of the Typhim Vi typhoid vaccine, the Imovax rabies vaccine, and other products. The company said it has already addressed the issues or is "working diligently" to address them and will correct them "in a timely way" with no vaccine supply disruption.

- **Stem cell research** – U.K. cardiologists plan to start a randomized trial of autologous stem cell injections in 90 patients with dilated cardiomyopathy. Researchers at Barts and the London Heart Attack Centre will take stem cells from each patient's hip. Then, in the active arm half the patients will get injections into their heart of their own stem cells, and the control patients will have their stem cells frozen and receive placebo injections. At the end of the study, the placebo patients will have the option of receiving an injection of their stem cells – provided the study is positive for the active arm.

- **THORATEC** terminated the agreement to sell its non-core International Technidyne Corporation (ITC) division, which manufactures and sells equipment for hemostasis management and point-of-care testing, to Danaher because of a disagreement over the status of ITC's quality systems and because the FDA did not approve ProTime InRhythm's 510(k) application. However, Thoratec still expects to sell ITC within the next 12 months.

NEWS IN BRIEF

BAUSCH + LOMB's PreserVision Eye Vitamin – recalled

Following reports of a small number of customers choking, B + L initiated a voluntary U.S. recall of this eye vitamin product. The problems occurred mostly in people over age 70 who reported difficulty swallowing and/or having a choking sensation when taking the soft gel.

Contact lenses
– account for a fourth of ER visits by children

An FDA study published in the journal ***Pediatrics*** found that more than 70,000 children/teens are seen in U.S. hospital emergency rooms each year for injuries and complications from medical devices, with contact lenses accounting for nearly a quarter of these (~17,000/year). Infections and eye abrasions were the most common contact lens wearer injuries – often the result of wearing the lenses too long without cleaning them. *The study is likely to lead to FDA action, perhaps labeling changes or public education efforts relating to contact lenses.*

Epilepsy Drugs
– only *some* may increase the risk of suicide

The FDA placed a suicide warning on all epilepsy drugs, but a new study published in the journal ***Neurology*** found that how much the newer drugs cause depression is linked to their suicidality potential. That is, the newer drugs that have a higher risk of causing depression than other epilepsy drugs, such as topiramate, were found to have a higher risk of suicidal behavior in epileptics. On the other hand, the newer drugs with a low risk of causing depression – such as gabapentin, as well as the older, conventional anti-epileptics – did not have any increased risk of self-harm or suicidal behavior.

The researchers studied 44,300 people in the U.K. General Practice Research Database who had epilepsy and ≥1 prescription for an epilepsy drug from 1989 through 2005, following them for 5.5 years. They found 453 had harmed themselves or attempted suicide, with 78 dying, and compared them to 8,962 patients who had not harmed themselves or attempted suicide. The patients using the newer drugs with a higher risk of depression were three times more likely to harm themselves or attempt suicide than those who were not currently taking any epilepsy drugs (1.3% vs. 0.5%).

The researchers said these results still need to be confirmed in additional studies but suggested they may help doctors and epileptics decide which drugs to use.

GLAXOSMITHKLINE's Braf-436 + Mek-183
– possible progress against melanoma

In a series of studies in 80 patients with advanced melanoma, more than half the patients taking Braf-436 saw their tumors reduced. Tumors also shrank in ≥50% of the patients who took Mek-183, with 25% seeing a 50% reduction in tumor size. The two drugs, which starve a tumor, are not a cure, but they may improve the quality of life and extend survival. They now will be tested in combination, Braf-436 QD and Mek-183 BID.

ICAGEN/PFIZER sodium channel pain program
– first-in-man study

A clinical study in healthy volunteers of several sodium channel (Nav1.7 or SCN9A) blocker compounds has been initiated to help select which of these should go forward. Pfizer is funding the collaboration, including research and preclinical development efforts, and has exclusive worldwide rights to commercialize any products that get approved.

LILLY's Effient (prasugrel) vs. SANOFI-AVENTIS's Plavix (clopidogrel)
– being studied head-to-head with and without a PPI

Medco Health Solutions is sponsoring a 104-patient trial in Paris that may finally determine which of these two anti-platelet drugs is best in coronary artery disease patients – whether or not they are on a proton pump inhibitor (PPI). The trial will have 4 arms, and the Plavix patients will have genetic testing performed.

1. Effient + Takeda's Prevacid (lansoprazole), a PPI.
2. Effient + placebo.
3. Double dose Plavix (150 mg) + Prevacid.
4. Double dose Plavix + placebo.

Medco hopes to learn whether using a double dose of Plavix overcomes the blunting effect of genetic factors (CYP2C19 polymorphism) or PPIs – or whether using Effient is a better strategy. The study results are expected in 2012.

Methylphenidate – may help cocaine addicts

A study reported in the ***Proceedings of the National Academy of Sciences*** suggests that intravenous administration of methylphenidate (a drug normally used for attention deficit hyperactivity disorder, ADHD) can help cocaine addicts resist the craving for cocaine. Yale University researchers used functional MRI to show that cocaine-dependent patients had robustly decreased stop signal reaction time ($p<0.0024$), but IV methylphenidate improved their cognitive control.

NEKTAR THERAPEUTICS' NKTR-102 (pegylated irinotecan)
– positive results in ovarian cancer

In a Phase II study, NKTR-102 given once every three weeks resulted in significant tumor shrinkage in women with advanced ovarian cancer, with 38% of patients having a marked reduction in the CA-125 biomarker. About 48% of

patients saw "sustained benefits" from the drug. NKTR-102 also is being tested in patients with metastatic breast cancer and colorectal cancer.

NOVARTIS's Gleevec (imatinib) – new lab test identifies resistant patients

Japanese scientists have developed a test they believe can accurately predict which chronic myeloid leukemia (CML) patients will be resistant to treatment with Gleevec. Resistance to Gleevec is relatively rare (2%-10% of patients) but serious. The study, which was published in the journal ***Clinical Cancer Research***, outlines a fluorescence resonance energy transfer biosensor used to measure the activity of leukemia cells. A researcher said the test is both sensitive and practical to use and is "especially useful for patients who are in relapse." The test, which is not available commercially in the U.S. appears to be pioneering work and a step in the direction of personalized medicine for CML patients. The study was funded by the Japanese government.

ONYX PHARMACEUTICALS' carfilzomib – positive multiple myeloma results

Positive results were reported by the company from a Phase II trial in 266 refractory multiple myeloma patients. Among patients who got carfilzomib, 36% had lower levels of monoclonal immunoglobulin, a protein, in their blood, and 24% had a reduction of ≥50%. The improvement lasted a median of 7.4 months. Onyx plans to submit carfilzomib to the FDA by the end of 2010 and seek accelerated approval.

OREXIGEN's Contrave (naltrexone + bupropion) – efficacy data published

A 1,453-patient, company-sponsored study published in ***The Lancet*** found that patients who took this diet pill (plus diet and exercise) lost 5%-6.1% of their body weight vs. 1.3% for patients on placebo. On average, patients on the high dose lost 13.4 pounds, and patients on the low dose lost 10.8 pounds vs. 3.1 pounds with placebo. Among completers, weight loss was 17 pounds (8.1%) with high dose and 14.3 pounds (6.7%) with low dose vs. 4.2 pounds (1.8%) with placebo.

In an accompanying editorial, Dr. Arne Astrup of Denmark said the experience with Abbott's Meridia (sibutramine) "perhaps suggests that more data are needed to get a better overall assessment of cardiovascular risk of this otherwise promising combination." One of his concerns with Contrave is blood pressure, which initially goes up and then drops slightly instead of going down significantly as usually occurs with weight loss.

Nausea was the most common side effect (30% high dose, 27% low dose), followed by headaches and constipation. The PDUFA date is January 31, 2011.

PFIZER's Chantix (varenicline) – more negative news

According to a paper in the ***Annals of Pharmacotherapy***, "Evidence is accumulating that the stop-smoking drug Chantix is linked with unprovoked acts and thoughts of aggression and violence...[The drug] is so potentially dangerous that its use should be restricted to exclude police, military, and similar occupations in which workers carry weapons." Of course, Pfizer disagrees.

Technetium-99 shortage – Congress could help but will it?

The American Society of Nuclear Cardiology, the American College of Cardiology, and a coalition of medical and national security organizations are asking Sen. Christopher "Kit" Bond (R-MO) to lift the hold on the American Medical Isotope Production Act (H.R. 3276) and allow the U.S. Senate to vote on the bill, which was passed in the House by a vote of 400 to 17. The legislation would encourage production in the U.S. of molybdenum-99 (Mo-99) – at least for medical isotopes. Mo-99 is the ore from which technetium is produced. That could help end the technetium-99 shortage. The legislation includes incentives such as government cost-sharing for production and government responsibility for final disposition of radioactive waste.

Currently, there are no technetium-99 suppliers in the U.S., making the U.S. dependent on a fluctuating worldwide supply. However, Sen. Bond argues that the bill could interrupt foreign production of isotopes prior to creating adequate domestic supplies.

FDA NEWS

FDA and FCC to collaborate on wireless devices

The FDA and the Federal Communications Commission (FCC) signed a Memorandum of Understanding, pledging to work together to promote the development and deployment of wireless technologies linking doctors, hospitals, and insurance companies. This is their first official partnership.

The FCC will work to get medical devices the spectrum they need, and both agencies will try to streamline the approval process and regulatory requirements for wireless healthcare IT device makers. Each agency will establish a liaison officer to be responsible for sharing information of mutual interest.

One issue that may get resolved with this new partnership: spectrum. There has been a dispute between healthcare IT and aeronautics companies over spectrums. Some health IT companies want to use 10 MHz of spectrum below the Wi-Fi spectrum with 20 milliwatt power to connect patient-worn monitors with the internet (Medical Body Area Networks or MBANs). The aeronautical companies have charged that this will create interference with airplane telemetry.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest

(*items in red are new since last week*)

Date	Topic	Committee
	August 2010	
August 11	**Valeant/GSK's Potiga** (ezogabine, formerly retigabine) for epilepsy	Peripheral and Central Nervous System Drugs Advisory Committee
August 17	**Momenta's generic enoxaparin**	U.S. Court for the District of Columbia hearing on Sanofi-Aventis suit to block the sale of this Lovenox generic
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 Postponed until November 2010	**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 16	**AstraZeneca's Brilinta** (ticagrelor)	PDUFA date
September 17 (not confirmed)	**Boehringer Ingelheim's Pradaxa** (dabigatran)	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 24	**Hologic's Selenia Dimensions** digital mammography tomosynthesis system	Radiological Devices Advisory Committee
	October 2010	
October 15	**Boehringer Ingelheim's Pradaxa** (dabigatran)	PDUFA date
October 22	**Arena Pharmaceuticals/Eisai's lorcaserin**, a diet drug	PDUFA date
October 22	**Lilly/Amylin's Bydureon** (exenatide long-acting)	PDUFA date
October 24	**Warner Chilcott's Actonel delayed-release** (risedronate)	PDUFA date
October 28	**Vivus's Qnexa** (phentermine + topiramate)	PDUFA date
	November 2010	
November 18	**Amgen's denosumab** for cancer patients	PDUFA date
	Other future meetings	
December 7	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	Endocrinologic and Metabolic Drugs Advisory Committee
January 31, 2011	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	PDUFA date
Date TBA	**Abbott's Meridia** (sibutramine), a diet drug	Endocrinologic and Metabolic Drugs Advisory Committee to review the SCOUT trial data
Date TBA, 2011	Review of accelerated drug approval process	Oncologic Drug Products Advisory Committee (ODAC)

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