Trends-in-Medicine

Quick Takes

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

SHORT TAKES

- **AMGEN's Prolia (denosumab) –** The U.K.'s National Institute for Health and Clinical Excellence (NICE) approved National Health Service coverage of Prolia to treat postmenopausal women at high risk of osteoporotic fracture who cannot take oral bisphosphonates.
- **Angioplasty balloons –** The FDA issued a rule saying that as of October 8, 2010, manufacturers of balloon-tipped coronary angioplasty catheters should use the 510(k) process to get them approved, rather than a PMA. The change is in line with the FDA's reclassification of percutaneous transluminal coronary angioplasty (PTCA) catheters from Class III to Class II devices.
- **ASTRAZENECA** agreed with Cancer Research U.K. and Cancer Research Technology (CRT) to take an experimental compound, called AZD-3965, which is one of a new class of cancer metabolism drugs, into early clinical trials. Under the agreement, AstraZeneca may decide on whether to develop the drug further based on the clinical trial data results at the end of the Phase I/IIa trial. AstraZeneca also signed a previous agreement with CRT in February for a three-year alliance to work on other projects.
- **ASTRAZENECA's Brilinta (ticagrelor) –** The FDA extended the PDUFA date by 3 months to December 7, saying it needed more time to review this blood thinner.
- **BOSTON SCIENTIFIC –** The FDA expanded approval of the company's implantable cardiac resynchronization therapy defibrillators (CRT-Ds) for a new indication – patients with mild or asymptomatic heart failure with left bundle branch block. Until now, CRT-Ds have only been approved to treat patients with more severe heart failure.
- **BRISTOL-MYERS SQUIBB** was warned by the FDA of possible sanctions if it fails to correct "significant violations" of good manufacturing practices at one of its two plants in Puerto Rico. The FDA said the plant "has not established or followed rules to prevent contamination of drugs" and alleged the problems indicate quality control weakness. Bristol was cited for similar problems in 2005 and 2009.

Among the drugs made at that plant are Orencia (abatacept) for rheumatoid arthritis and the blood thinner Coumadin (warfarin).

The 483 letter has the potential to delay approval of pending new drugs until the issues are resolved.

- **Carotid Stenting –** A meta-analysis published in ***The Lancet*** found that the risks and harms of carotid stenting vs. endarterectomy increase as patients get older, and stenting should be avoided in patients ≥70 years old.

- **Dextromethorphan –** The FDA's Drug Safety and Risk Management Advisory Committee voted 15-9 against requiring a prescription for Pfizer's Robitussin, Johnson & Johnson's Tylenol Cold Tablets, and other over-the-counter cough medicines that contain dextromethorphan. Panel members said dextromethorphan abuse is a concern among adolescents, but the drug does not pose enough of a threat to make it a controlled substance.

- **Embryonic stem cells –** The National Institutes of Health has resumed studies, grants, and assessment of funding for embryonic stem cell research, after a U.S. Court of Appeals temporarily lifted a ban on the research by a lower court.

- **GENMAB/SEATTLE GENETICS** entered into an antibody-drug conjugate (ADC) research collaboration agreement. Genmab has the rights to use Seattle Genetics' ADC technology with its HuMax-TF antibody targeting the Tissue Factor antigen, which is expressed on many types of solid tumors. Seattle Genetics has the right to exercise a co-development option for any resulting ADC products at the end of Phase I clinical development.

- **GENZYME** is cutting jobs to reduce costs, but the company did not say how many of the 12,800 employees will be let go.

- **GENZYME's Fabrazyme (agalsidase beta) –** The company said the shortage of this Fabry disease treatment, which has caused rationing, is likely to end in 1H11. Genzyme also expects dosing of Cerezyme (imiglucerase) to return to normal in 4Q10.

- **HARBOR BIOSCIENCES' apoptone (HE-3235) –** Data from an ongoing Phase I/IIa trial in castration resistant prostate cancer (CRPC), suggest this novel steroid analog of a testosterone metabolite may be promising. Of the 22 patients randomized to 100 mg or 350 mg apoptone, one patient had a confirmed partial overall response. Principal investigator Dr. Bruce Montgomery of the University of Washington School of Medicine said, "This is an exciting finding because, at the 350 mg dose, we are seeing a quantitative response…Further dose escalation is justified to explore the promise of activity at higher serum concentrations." Dose escalation to 700 mg has been initiated in the trial.

- **ICAGEN's ICA-105665 –** Enrollment was suspended in a photosensitivity study of this small molecule (an activator of certain subtypes of KCNQ ion channels) due to an adverse event which occurred in the 600 mg patient cohort following completion of the 500 mg patient cohort. No serious adverse events were noted in the completed ascending dose study in healthy volunteers at daily doses of 500 mg and 600 mg for seven days. A final review of lab data is ongoing.

- **IMMUNE NETWORK** is acquiring technology from **Immunitor** for making and delivering oral vaccines for infectious diseases.

- **INCYTE/NOVARTIS's INCB-18424**, a Jak inhibitor, was effective in a 153-patient Phase II study in myelofibrosis published in the ***New England Journal of Medicine***, and the company has started Phase III trials. In the Phase II study, INCB-18424 shrank spleens by at least 50% in 44% of patients. Patients also had reduced symptoms, gained weight, and had more exercise capability.

- **Intra-aortic balloon pump (IABP) –** Patients with advanced heart failure achieved adequate circulatory support and ambulation after axillary-subclavian placement of an IABP, indicating it may offer some advantages over femoral placement, according to a retrospective review reported at the Heart Failure Society of America (HFSA) meeting.

- **JOHNSON & JOHNSON –** The senior executive at J&J in charge of the troubled consumer product division, Colleen Goggins, will retire early next year. And a House committee has asked CEO William Weldon to testify at a hearing on September 30 about the company's handling of the recall of liquid children's Tylenol and a "phantom" recall of Motrin.

- **JOHNSON & JOHNSON** is in advanced negotiations to buy the rest of the shares of Dutch vaccine manufacturer, **Crucell**, that it doesn't already own, giving J&J a vaccine platform.

- **LILLY –** A New York federal appeals court reversed a 2008 ruling that had granted class-action status to a suit by pension funds, unions, and insurers claiming that improper marketing of Zyprexa (olanzapine), a schizophrenia medication, raised their costs.

- **NOVARTIS's Gilenia (fingolimod)** – Russian health authorities were the first to approve this oral drug for relapsing remitting multiple sclerosis. An FDA decision is expected September 21, 2010.

- **Oral anti-viral medications –** In a retrospective study published in the ***Archives of Ophthalmology***, oral anti-viral medications were associated with a reduced risk of recurring eye disease – e.g., epithelial keratitis, stromal keratitis, blepharitis, or conjunctivitis – caused by herpes simplex virus.

- **PFIZER's Inspra (eplerenone) –** Researchers reported at the HFSA meeting that patients with diastolic heart failure had mixed results when treated with this aldosterone receptor antagonist. Their diastolic function improved and markers of collagen turnover declined significantly after six months of treatment, but exercise capacity and quality of life did not improve.

- **ROCHE's taspoglutide –** The company has stopped all administration of this Type 2 diabetes drug because of an excessively high dropout rate in the Phase III studies due to side effects, primarily nausea and vomiting. Roche said it is trying to figure out what caused the side effects and how to ***reformulate*** the medication. However, Roche said it is not abandoning the drug, though the reformulation may cause a significant delay.

- **ROCHE/GENENTECH's Valcyte (valganciclovir hydrochloride)** – The FDA changed the label for this anti-viral agent to warn about possible overdose in pediatric patients undergoing a kidney or heart transplant and to add an upper dosing limit of 150 mL/min/1.73 m^2 to the creatinine clearance level.

- **SAVIENT PHARMACEUTICALS' Krystexxa (pegloticase)** was approved by the FDA for IV infusion every two weeks to treat gout in adults who do not respond to or who cannot tolerate conventional therapy such as the xanthine oxidase inhibitors Prometheus Labs' Zyloprim (allopurinol) and Takeda's Uloric (febuxostat). The FDA is advising doctors using Krystexxa to give patients a corticosteroid and an antihistamine beforehand to minimize the risk of severe allergic reaction and to be cautious about administering the drug to patients with congestive heart failure.

- **SHIRE PHARMACEUTICALS** is collaborating with **Acceleron Pharma** to develop and commercialize treatments for rare muscular and neuromuscular disorders.

- **SINOBIOMED** is acquiring the assets of **i-Media Asia**, with the transaction expected to be completed in 4Q10.

- **TEVA's Copaxone (glatiramer acetate) –** Adding albuterol to Copaxone failed to boost the efficacy of Copaxone in a 24-month, 44-patient, randomized trial in multiple sclerosis. The study, which was published in the ***Archives of Neurology***, missed the primary endpoint – a change in MS Functional Composite score – but composite functional scores were significantly improved at 6 and 12 months vs. placebo. The addition of albuterol also delayed the time to first relapse.

- **WESTMED's BagEasy Manual Resuscitation Device –** The FDA issued a Class I recall on certain lots of this device, saying they had an error which may render them inoperable and delay needed treatment. The device's retention ring may become disconnected, preventing delivery of treatment and requiring an alternate method of resuscitation.

NEWS IN BRIEF

ALKERMES' Vivitrol (naltrexone extended-release injection) – gets positive ruling from FDA panel

The FDA's Psychopharmacologic Drugs Advisory Committee voted:

- 11 to 2 that it is an effective treatment for opioid dependence.
- 10 to 1 (with 2 abstentions) that the trial results can be applied to the U.S. population.
- 12 to 0 (with one abstention) that the safety data are adequate.
- 12 to 1 that it should be approved.

AMGEN's Aranesp (darbepoetin) – response, not just hemoglobin level, matters

A study published in the ***New England Journal of Medicine*** found that patients with chronic kidney disease, Type 2 diabetes, and anemia – and not on dialysis – who had a poor initial response to Aranesp had an increased risk of adverse cardiovascular (CV) outcomes and death in the 4-year TREAT study. Poor responders were 31% more likely to have a CV event or die. The researchers said the findings "raise the question of whether the degree of hematopoietic responsiveness to ESA (erythropoiesis stimulating agent) treatment, and not just the target hemoglobin level," should be considered in ESA therapy.

CELL THERAPEUTICS' pixantrone – company to appeal FDA rejection

Earlier this year, an FDA advisory committee unanimously voted against approval of this non-Hodgkin's lymphoma therapy and recommended the company conduct another trial to demonstrate the drug's safety and efficacy, and the FDA followed the panel's advice. The company said that it plans to appeal the FDA decision because "there are no alternatives for some NHL patients other than pixantrone."

EMISPHERE TECHNOLOGIES' Eligen technology – helps deliver digestive hormones

Eligen effectively facilitated the oral administration of SNAC along with two low oral bioavailability digestive hormones in a study published in the ***American Journal of Clinical Nutrition***. Food intake was reduced 21.5% and satiety increased ($p<0.05$) in the 12 healthy male volunteers tested in a randomized double-blind, placebo-controlled, 4-way crossover trial. Researchers reported that both digestive hormones (GLP-1 and PYY3-36) were rapidly absorbed from the gut, leading to plasma concentrations several times higher than those in response to a normal meal. GLP-1 alone, but not PYY3-36, significantly reduced total food intake.

FOREST LABORATORIES – pleads guilty

Forest is paying more than $313 million to settle criminal and civil complaints that it illegally promoted off-label use of its antidepressant Celexa (citalopram) for use in children and adolescents. Celexa was approved only to treat adult depression. The government also claimed that Forest publicized the positive results of a study on Celexa in adolescents while failing to tell doctors about a similar study that had negative results.

Forest also pled guilty to misdemeanor charges for distributing the thyroid drug Levothroid (levothyroxine) before it was approved. The case also alleged that Forest paid kickbacks to doctors to encourage the prescribing of Celexa and Lexapro (escitalopram oxalate). Forest also reportedly concealed information about its testing of Levothroid, distributed it in quantities far exceeding amounts that federal drug regulators permitted, and failed to advise CMS that the drug no longer qualified for coverage by government health programs, causing false claims to be submitted to those programs.

H1N1 flu – new resistance information

Two studies in the journal ***Emerging Infectious Diseases*** reported on different types of resistance that has been seen in H1N1.

1. The first article speculated that co-infection with seasonal influenza A (H1N1) and pandemic (H1N1) could result in the emergence of a harmful new strain of the virus that could be resistant to treatment. The researchers believe that this warrants further investigation in animal models or *in vitro*.
2. Another study reported on a woman in Singapore who developed resistance to Tamiflu (oseltamivir) very quickly – within 48 hours. The researchers recommended that clinicians consider resistance if patients don't respond to treatment for pandemic H1N1.

Memory loss – more than just forgetfulness in old age

Forgetfulness in older people may be an early sign of dementia or Alzheimer's disease, not just old age. According to a study published in ***Neurology***, the medical journal of the American Academy of Neurology, the same brain lesions associated with dementia are responsible for mild memory loss in old age.

The study author, Robert Wilson, PhD, of Rush University Medical Center said "It appears these brain lesions have a much greater impact on memory function in old age than we previously thought. Our results challenge the concept of normal memory aging and hint at the possibility that these lesions play a role in virtually all late-life memory loss."

The study, which was supported by the National Institute on Aging, followed 350 Catholic nuns, priests, and brothers for 13 years. After death, their brains were autopsied. The researchers found that memory decline tended to be gradual but speeded up in the last four to five years of life. Tangles, Lewy bodies, and stroke were all related to gradual memory decline. Almost no gradual decline was seen in the absence of tangles.

This discovery could lead to new treatments to delay memory loss in old age.

NEUROCRINE BIOSCIENCES/GLAXOSMITHKLINE's GSK-561679 – failed in Phase II trial

In a 6-week, 150-patient study vs. placebo in patients with major depressive disorder, this corticotropin releasing factor (CRF1) receptor antagonist showed no benefit over placebo. The companies are also testing the drug in post-traumatic stress disorder (PTSD), anxiety, and alcoholism. After the failed trial, the companied will re-evaluate the future of the drug.

OSPREY MEDICAL
– possible solution to contrast media toxicity

According to a study reported in the ***Journal of the American College of Cardiology***, Osprey has developed a way to successfully and safely remove contrast media (by aspiration from the coronary sinus) in patients undergoing coronary angiography and intervention. The procedure reduced systemic exposure and nephrotoxicity. In the study, the coronary sinus was successfully cannulated with an aspiration catheter in 31 of 41 patients, with the mean time 11 minutes and no device-related serious adverse events. In the patients in whom the contrast media were removed, the estimated glomerular filtration rate (eGFR) remained steady out to 72 hours post-procedure, while it decreased significantly in patients without contrast removal. A large, randomized trial is still needed to validate the approach, but researchers were encouraged with this study.

PFIZER/BOEHRINGER INGELHEIM's Spiriva (tiotropium bromide) – possible therapy for poorly controlled asthma

This chronic obstructive pulmonary disease (COPD) drug successfully treated adults whose asthma was not well-controlled on low doses of inhaled corticosteroids in a study published in the ***New England Journal of Medicine*** and presented at the annual congress of the European Respiratory Society in Barcelona, Spain.

The 210-patient, 48-week study, which was supported by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health, found that adding Spiriva to low-dose inhaled steroids was more effective at controlling asthma than doubling the steroid dose and as effective as adding the long-acting beta agonist salmeterol (GlaxoSmith-Kline's Serevent). Dr. Stephen Peters of Wake Forest

University Baptist Medical Center, the principal investigator, said further analysis is needed to determine which patients respond best to Spiriva and then longer-term studies will be needed to establish safety and the effect on the frequency and severity of asthma exacerbations.

TAKEDA's Actos (pioglitazone) – both bad news and good news

- **Bad news – FDA reviewing safety.** The FDA has begun a safety review of this diabetes drug, focusing on the risk of bladder cancer, after 5-year data from an ongoing 10-year observational study showed an increased risk of bladder cancer in patients with the longest exposure to Actos and in those with the highest cumulative dose of the drug. The FDA also said that studies in animals and humans suggest this is a potential safety risk that needs further study.

  Perhaps this is why the FDA has not made a final decision on whether to pull GlaxoSmithKline's Avandia (rosiglitazone) from the market, restrict its use, or just strengthen the label further.

- **Good news** – Actos appears safe as a treatment for Alzheimer's disease – yes, AD not just diabetes. A 29-patient pilot trial published in the ***Archives of Neurology*** showed Actos is safe and well-tolerated in AD patients, setting the stage for larger efficacy trials. The trial, which was supported by a grant from the National Institute on Aging, was not powered to show efficacy, but there was little difference in cognitive score on ADAS, suggesting that future trials will be in early disease, not mild-to-moderate AD. Patients in future trials will have to be monitored for peripheral edema (which occurred in 28.6% of the AD patients), heart failure, and other CV morbidities. GlaxoSmithKline's Avandia (rosiglitazone) had some promising initial results in mild AD but failed overall in a large trial.

FDA NEWS

FDA asked to extend deadline for 510(k) reform comments

AdvaMed and some state medical device associations have asked the FDA to extend the comment period on its proposal for 510(k) reform by 30 days. The current deadline is October 4, 2010.

FDA and CMS proposing parallel reviews of drugs and devices

The FDA and the Centers for Medicare and Medicaid Services (CMS) are considering establishing a process for overlapping evaluations of FDA-regulated medical products (drugs and devices) ***when the sponsor and both agencies agree*** to the parallel review. The parallel review would be designed to reduce the time between FDA approval/clearance and CMS national coverage determinations (NCDs). The agencies are seeking public comment for 90 days on what products would be appropriate for parallel review, what procedures should be developed, how a parallel review process should be implemented, and other issues related to the effective operation of the process.

FDA and CMS also announced their intent to create a pilot program for parallel review of medical devices that will begin after both agencies have reviewed the public comments on this notice. A memorandum of understanding (MOU) concerning the exchange of data and information has been completed between the two agencies.

For more details see:
www.fda.gov/AboutFDA/Partnerships&fxsp0;Collaborations/Memorandaof&fxsp0

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 20	**Boehringer Ingelheim's Pradaxa** (dabigatran), an anticoagulant	FDA's Cardiovascular and Renal Drugs Advisory Committee
September 21	**Novartis's Gilenia** (fingolimod)	Revised PDUFA date
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 4	**FDA 510(k) reform comments**	Deadline for public comments
October 8	Clinical trial design recommendations for **devices for the treatment of depression**	FDA's Neurological Devices Advisory Committee
October 12	**Alkermes' Vivitrol** (naltrexone ER injection) for opioid dependence	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 16	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	FDA's Arthritis Advisory Committee
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	PDUFA date
	December 2010	
December 7	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
December 7	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	New PDUFA date
December 7	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
December 9	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	PDUFA date
December 17	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	Revised 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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