Trends-in-Medicine

Quick Takes

by Lynne Peterson

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Check out the *Trends-in-Medicine* blog on our website (**www.trends-in-medicine.com**).

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

SHORT TAKES

- **ACCELERON PHARMA'S ACE-031** was granted fast-track status by the FDA as a potential treatment for Duchenne muscular dystrophy.
- **AFFYMAX/TAKEDA'S Hematide (peginesatide) –** The companies plan to submit Hematide to the FDA in 1H2011 for the treatment of anemia in dialysis patients and will continue to study the drug in non-dialysis patients.
- **ALKERMES' Vivitrol (naltrexone for extended-release injectable suspension)** for the treatment of opioid dependence will be reviewed by the FDA's Psychopharmacologic Drugs Advisory Committee on September 16, 2010.
- **ALLERGAN's Botox (onabotulinumtoxinA) –** The FDA has extended its review of Botox for migraine headaches after the company provided FDA-requested information on safety monitoring, physician training, and the proposed Medication Guide and Dear Healthcare Provider letter. The new PDUFA date is in October 2010.
- **ASCENDIS PHARMA –** Novo Nordisk, Novartis/Sandoz, and Lilly are reportedly among the bidders for this Danish pharma. Ascendis has controlled-release drug technology that these bidders want, and it is developing both a once-weekly growth hormone and a once-weekly insulin injection.
- **AXCAN SCANDIPHARM's Photofrin (porfimer sodium) –** The FDA issued a warning letter about success stories on the company's website that "overstated the efficacy" and made "unsubstantiated claims" about this treatment for non-small cell lung cancer (NSCLC) in patients for whom surgery and radiotherapy are not indicated.
- **BAYER's Xarelto (rivaroxaban) –** Top-line data from the EINSTEIN-DVT trial showed that Xarelto was non-inferior to warfarin in preventing blood clots in the lung and legs with comparable major/minor bleeding. However, the net clinical benefit (efficacy plus major bleeding) was significantly better than placebo. The

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full EINSTEIN-DVT results will be presented at the European Society of Cardiology meeting on August 31, 2010. Xarelto is approved in Europe, but the FDA has requested additional information, which likely means the results of the ongoing ROCKET-AF trial.

- **DENDREON's Provenge (sipuleucel-T) –** The FDA sent the company a warning letter saying Provenge promotional materials "are false or misleading because they omit and minimize the risk and overstate the efficacy of Provenge." The offending items include a chart that "does not provide sufficient contextual information" on the survival rate. Dendreon, not surprisingly, said it intends to comply with the FDA requests.

- **DEPOMED's AcuForm –** Johnson & Johnson/Janssen was granted a non-exclusive license to this gastric retentive drug delivery technology for the development of a fixed dose combination formulation of canagliflozin, an SGLT2 inhibitor plus extended-release metformin. J&J also was granted a right of reference to the Glumetza (extended-release metformin) NDA and associated data for use in developing the combination product.

- **ENTEROMEDICS' Maestro RC System** received approval from the FDA to start a clinical trial of this vagus nerve stimulator for obesity, but the company still needs to find funding to conduct the study. Maestro received a CE Mark in 2009, and the company hopes to file for approval in Australia soon.

- **GERON's GRNOPC1 –** The FDA approved restarting a study of GRNOPC1, an embryonic stem cell-based therapy, in patients with new spinal cord injuries, and the company hopes to start enrolling new patients by the end of this year. A total of 8-10 patients will be enrolled, and each patient will be followed for a year, so the trial is expected to take ~2 years to complete. The company had started the study in early 2009, but it was stopped due to concerns in an animal study that showed an excess of small cysts at the injury site. GRNOPC1 was developed by Geron and the University of California, Irvine.

- **GLAXOSMITHKLINE** has partnered with **FivePrime Therapeutics**, a privately-held drug developer, giving GSK the option to develop drugs discovered by FivePrime as treatments for skeletal muscle disorders like sarcopenia and cachexia.

- **GLAXOSMITHKLINE's GSK-299423 –** Researchers reported in the journal ***Nature*** on very early results with this promising new antibiotic that works similarly – but differently – from quinolones and may be effective against antibiotic-resistant bacteria.

- **ISOTECHNIKA/LUX BIOSCIENCES' voclosporin –** The FDA asked for another trial before approving this non-infectious uveitis therapy, and Lux Biosciences said it is ready to start that study. The drug currently is under review by European regulators.

- **JERINI's icatibant** was effective in reducing swelling associated with angioedema in one Phase II trial but failed to meet the primary endpoint in another Phase II trial. Both randomized, double-blind trials, which included a total of 130 patients, showed the drug to be safe. The results were published in the ***New England Journal of Medicine***. A Phase III trial is underway.

- **Ketamine** may be a promising treatment for depression in bipolar patients. A small (18-patient) study conduced by researchers at the National Institute of Mental Health, published in the ***Archives of General Psychiatry***, found that 71% of bipolar patients who had not responded to other treatments had significant improvement in depression symptoms after a single intravenous infusion of 0.5 mg/kg ketamine. Most of these patients responded within 40 minutes, with the effects lasting for ~3 days. This is an off-label use of ketamine.

- **LASIK surgery centers –** Five LASIK centers received FDA warning letters in April 2010 saying that they did not properly disclose information about their laser eye surgery operations. The sites include Lasik Vision Institute in Boca Raton, FL.

- **MEDICARE –** Treasury Sec. Timothy Geithner and HHS Sec. Kathleen Sebelius held a press conference and claimed that healthcare reform will improve Medicare's long-term finances, but the media remain skeptical. None of the television news networks even mentioned the press conference, and the print journalist headlines used words such as: "projections in dispute," "maybe," "doubted."

- **MERZ's Xeomin (incobotulinumtoxinA, NT-201)** was approved by the FDA for two indications – cervical dystonia and blepharospasm – but not for spasticity. Xeomin was approved in Canada early in 2009 for all three indications. Xeomin does not require refrigeration as does Botox, and it is reconstituted 1:1 like Botox, which gives it an advantage over Medicis' Dysport (ababotulinumtoxinA).

- **Multiple sclerosis (MS) –** A study reported in the American Academy of Neurology's journal, ***Neurology***, found that a gene variant may increase the severity of MS. Researchers screened the oligoadenylate synthetase (OAS) gene in 401 MS patients, 394 people without MS, and 178 MS patients taking beta interferon. They found that MS patients with the AA genotype had earlier relapses and increased disease activity vs. those without that genotype. The study also found people who had the GG genotype had less disease activity and fewer relapses.

- **NICOX** will shut down its U.S. headquarters by the end of August 2010 since the FDA rejected its pain drug, naproxcinod. The company is talking with the FDA about what would be needed for approval, and it still plans to seek approval in Europe.

- **ROCHE/GENENTECH** has expanded its deal with **Seattle Genetics** for antibody-drug conjugate technology.
- **SHIRE** is purchasing **Movetis**, which will expand Shire's gastrointestinal (GI) market presence in Europe, where Movetis sells Resolor (prucalopride) for chronic constipation in women without adequate relief from laxatives. The U.K.'s NICE recently approved Resolor as an option for women who have already tried at least two different types of laxative without success.
- **TARGACEPT** has licensed rights to **Cornerstone Therapeutics**' library of preclinical compounds as well as its potential NNR-based drugs for inflammatory conditions.
- **TEVA PHARMACEUTICAL INDUSTRIES** has been cleared by Canadian authorities to complete its acquisition of **Ratiopharm**, a German generic drug firm.
- **XOMA's XOMA-052**, an antibody to interleukin-1 beta for the treatment of uveitis associated with Behcet's disease, has been granted orphan drug status by the FDA. European regulators previously granted orphan drug status as well.
- **ZIMMER** was asked by Sen. Charles Grassley (R-IA) to provide information on how it monitors the long-term performance of its artificial hips and knees and how it handles feedback and complaints from surgeons.

NEWS IN BRIEF

Centers for Medicare & Medicaid Services (CMS)

- **Payments to hospitals to change in 2011.** Acute care hospitals will receive 0.4% ***less*** ($440 million less) for inpatient stays under the proposed Inpatient Prospective Payment System (IPPS) rule. Long-term care hospitals (where patients typically stay >25 days) will see a 0.4% ***increase*** ($22 million more).
- **PET reimbursement changed.** Previously, CMS paid for only one PET scan for treatment planning in patients with solid tumors and myeloma. In a new decision memo, CMS said it no longer believes that policy is justified and will change the National Coverage Decision (NCD) to remove the one-scan restriction. While CMS nationally will cover one scan, local carriers now can decide if they want to cover more than one scan.

Finasteride – adoption slow for prostate cancer prevention

In 2003, the Prostate Cancer Prevention Trial (PCPT) showed a significant 25% reduction in prostate cancer in men taking finasteride, but physicians have not increased its use of the drug, according to a study published in ***Cancer, Epidemiology, Biomarkers & Prevention***, a journal of the American Association for Cancer Research (AACR). The authors of the usage study suggested that the problem may be an editorial that accompanied the publication of the 2003 results, mentioning a 27% increased risk in high-grade tumors. Dr. Ian Thompson, chairman of the department of urology at the University of Texas Health Science Center, who led the usage study, said the editorial may have colored the perception of finasteride, "The study paradox of a reduction in overall disease but an increase in high-grade disease was not explored until much later."

In 2008, another report was published in ***Cancer Prevention Research***, another journal of the AACR, where Thompson and colleagues reanalyzed the PCPT data as well as the available tumor biopsies and showed that finasteride did not actually increase the risk of high-grade tumors, just making the available testing more sensitive. This result confirmed the benefits of finasteride for prostate cancer prevention.

However, results of this new usage survey of 325 urologists and 1,200 primary care physicians found that physicians have not changed their practice patterns. Although the number of men starting finasteride grew over a five-year period, the publication of the PCPT trial did not influence their decision:

- 57% of urologists and 40% of primary care physicians said they prescribed finasteride more often.
- Only 2% said they had been influenced by the findings in PCPT.
- 64% of urologists and 80% of primary care physicians ***never*** prescribe finasteride for chemoprevention.
- Among doctors who do not prescribe finasteride for chemoprevention, 55% said they were concerned about the risk of high-grade tumors and 52% said they did not know it could be used for chemoprevention.

GENZYME's Fabrazyme (agalsidase beta) – HHS asked to break patent

Three Fabry patients have petitioned the Department of Health and Human Services (HHS) to let other companies manufacture Fabrazyme because Genzyme has not been able to meet demand due to manufacturing problems. The patients want HHS to use its "march-in" authority to break the Genzyme patent and license other manufacturers to produce the drug.

Fabry disease is an inherited enzyme deficiency that can cause heart and kidney problems, as well as pain and other symptoms. During the drug shortage, patients have been receiving about a third of their usual doses, and many say they are experiencing increased pain, gastrointestinal problems, and other symptoms. One patient may even have died as a result of the inability to get enough Fabrazyme.

The petitioners claim HHS has the authority to break the Genzyme patent because the National Institutes of Health (NIH) financed the research at Mount Sinai School of Medicine,

which gave an exclusive license to Genzyme. The petition proposes that Genzyme get a 5% royalty on sales by other manufacturers.

The government has rejected similar petitions for other drugs, so the outlook for this petition is not good, and even if the petition were granted, it would take time for other manufacturers to gear up and produce Fabrazyme.

GENZYME/ISIS' mipomersen – effective at lowering LDL cholesterol but safety issues

In top-line data from two double-blind, placebo-controlled, 26-week Phase III trials, mipomersen (an antisense drug given as a once-weekly injection) met the primary endpoint, lowering LDL in patients already on maximal statin therapy. However, ≥20% of patients in each trial dropped out due to adverse events, and 10%-15% of patients had elevated liver enzymes. The companies plan to submit mipomersen to the FDA in 1H11 for the treatment of homozygous familial hypercholesterolemia and ***perhaps*** severe hypercholesterolemia.

- **Severe hypercholesterolemia study** – included 58 patients from 26 sites in North America, Europe, and South Africa. The trial met all three secondary endpoints, with statistically significant reductions in apo-B, non-HDL-cholesterol, and total cholesterol. There were no Hy's Law cases.
- **High cholesterol and high cardiovascular risk study** – included 158 patients (half Type 2 diabetics) from 43 sites in the U.S. and Canada. Half the mipomersen patients achieved LDL <70. The trial met all three secondary endpoints, with statistically significant reductions in apo-B, non-HDL-cholesterol, and total cholesterol. In "many cases" the ALT elevations were associated with increased hepatic fat content (on MRI), but there were no Hy's Law cases.

Phase III Results with Mipomersen in Hypercholesterolemia

Measurement	Mipomersen 200 mg weekly	Placebo	p-value
Severe hypercholesterolemia (n=58)			
Number of patients	39 patients	19 patients	---
Completers	27 patients (69%)	18 patients (95%)	---
Discontinuations due to adverse events	8 patients (20.5%)	1 patient (5%)	---
Death	1 patient *	0	---
ALT >3xULN	15%	N/A	---
Primary endpoint: LDL reduction	36% (101 mg/dL)	13%	<0.05
High cholesterol and high cardiovascular risk (n=158)			
Number of patients	105 patients	53 patients	---
Completers	60 patients (57%)	44 patients (83%)	---
Discontinuations due to adverse events	26 patients (25%)	2 patients (4%)	---
Death	0	1 patient **	---
ALT >3xULN	10%	N/A	---
Primary endpoint: LDL reduction	37% (48 mg/dL)	5%	<0.05

* Due to acute coronary syndrome, deemed unrelated ** Due to MI

The ALT elevations may not be as big a problem as some critics are charging in light of comments by FDA officials about drug-induced liver toxicity. See the recent ***Trends-in-Medicine*** *report on Drug-Induced Liver Injury.*

HPV vaccine – survey finds use skewing to older girls

A national survey of primary care physicians found that doctors are being more aggressive in getting older teenage girls immunized with the HPV vaccine than the 11 to 12 year olds who are the key target for the vaccine. In the survey, published in the journal ***Pediatrics***, the 848 respondents indicated:

- 98% of pediatricians and 88% of family physicians administer the HPV vaccine in their offices.
- 90% of pediatricians and 86% of family physicians strongly recommend the vaccine to 13- to 15-year-old patients.
- 57% of pediatricians and 50% of family physicians urge vaccination of 11- to 12-year-old girls.
- Parent refusal and the need to discuss sexuality issues were the principal reasons for not making a harder push for the vaccine in younger girls.
- Key barriers to HPV vaccination are cost and insurance coverage.
- ~50% incorrectly thought that the incidence of HPV is highest among women in their 30s.
- ~60% of pediatricians and 42% of family physicians incorrectly said genital warts and cervical cancer were caused by the same HPV types.

TAKEDA's azilsartan (AZL-M, TAK-491) – better results in African Americans than Caucasians

The results of a Phase III trial were presented at the National Medical Association meeting, and they showed that this new

Azilsartan Results in African Americans

Measurement	Azilsartan 40 mg	Azilsartan 80 mg	Placebo
Ambulatory 24-hour mean SBP	- 7.7 mmHg (p≤0.001)	- 10.5 mmHg (p≤0.001)	- 2.7 mmHg
Clinic SBP	- 6.5 mmHg (p≤0.001)	- 6.5 mmHg (p≤0.001)	N/A
Ambulatory DBP	- 4.9 mmHg (p≤0.001)	- 7.3 mmHg (p≤0.001)	N/A
Discontinuations due to headache	5 patients		N/A

angiotensin II receptor blocker (ARB) works well in African Americans but not as well in Caucasians. The randomized, 6-week study tested two doses (40 mg and 80 mg) vs. placebo in 289 African Americans with mild-to-moderate primary hypertension. The most common adverse event was headache. Azilsartan was submitted to the FDA in April 2010.

TNF inhibitors – may increase cancer risk in children

A study, published in the journal ***Arthritis & Rheumatism***, found that the use of TNF-alpha inhibitors – Johnson & Johnson's Remicade (infliximab), Amgen's Enbrel (etanercept), and Abbott's Humira (adalimumab) – in children may increase the risk of malignancy, particularly when the drugs are given for inflammatory bowel disease rather than for rheumatic conditions. The authors said 48 cases of malignancy have been reported among children and young adults taking these biologics, although no clear causal relationship could be established since most of the children were on multiple immunosuppressive drugs, and the underlying risk for malignancy with autoimmune disease is not clear.

Transcatheter aortic valve implantation (TAVI)

A study sponsored by the Agency for Healthcare Research and Quality (AHRQ) found that TAVI may be appropriate for patients who cannot tolerate surgical valve replacement, especially older or sicker patients. But AHRQ said additional research is needed to understand the potential risks and benefits, particularly in the long term. The study was conducted by Duke Evidence-based Practice Center and published in ***Annals of Internal Medicine***. The researchers examined 62 published studies with a total of 856 patients – as well as other studies not yet published – using seven different percutaneous valves, but they did not conclude any valve is safer or more effective than the others.

FDA News

The FDA seeking more comments on neurological device reclassification

The FDA decided to reopen the period for accepting public comments on a proposal to reclassify certain types of neurological and physical medicine devices from Class III, or high-risk, to Class II, or medium-risk. The new deadline for comments is September 7, 2010.

FDA Advisory Committee split over changing trial endpoints midstream

The Cardiovascular and Renal Drugs Advisory Committee voted 7-6 that the FDA should allow Pfizer to retroactively change the primary endpoint in a pediatric trial of Revatio (sildenafil) in pulmonary arterial hypertension. Dr. Robert Temple, deputy director for clinical science in the FDA's Center for Drug Evaluation & Research (CDER), told the panel, "We don't usually allow you to change the endpoints after you've seen the data," but he added that doing so is not unprecedented.

The problem in the Pfizer trial was that the 6-minute exercise test used for adults couldn't be used as planned in children. The FDA suggested that Pfizer use the secondary endpoint – pulmonary vascular resistance index (PVRI) – as the primary endpoint. *It is unlikely that this decision reflects any change in policy by the FDA on primary endpoints.*

FDA proposed REMS for long-acting/extended-release opioids too weak

Critics have charged that the FDA's long-awaited risk evaluation and management strategy (REMS) for opioids is too weak. ***MedPageToday*** conducted a survey of its readers to see what they thought should be done to curb misuse and abuse of opioids, and the results were very critical of the FDA's proposed REMS.

- 21% said ***current policy*** is sufficient.
- 32% said the FDA should ***require*** training for providers who prescribe opioids. *This is not a part of the REMS the FDA proposed.*
- 34% said there should be a ***registry*** of patients using opioids. *This is not a part of the REMS the FDA proposed.*
- 1% said a ***new federal agency*** should be created to deal with the problem.
- 12% said ***another solution*** needs to be found.

FDA workshop on cystic fibrosis drug development

The FDA is holding a public workshop on September 23-24, 2010, on scientific issues in clinical development of aerosolized antimicrobials for the management/treatment of patients with cystic fibrosis (CF). The workshop is intended to provide information for and gain perspective from healthcare providers, patients and patient advocacy organizations, academia, and industry on various aspects of ***clinical trial design*** of aerosolized antimicrobials in CF patients. The FDA plans to use the input from this workshop to help develop topics for further discussion.

Legislation introduced to give FDA new authority

Sen. Michael Bennet (D-CO) introduced legislation that would give the FDA more enforcement powers. The bill – the Drug Safety and Accountability Act of 2010 – would require companies to document each contributor to their products, would give FDA subpoena power when conducting investigations, and would give the FDA the new authority to recall drugs when safety issues arise. The legislation also would enhance the FDA's data systems to track all global manufacturers supplying drugs and drug ingredients.

Sen. Bennet cited a "record 1,742 drug recalls" in 2009 – "a 400% increase" from 2008, and said that 80% of the active ingredients in U.S. drugs are made outside this country. He also cited the results of a Pew Prescription Project survey which he said found:

- 70% of respondents have little or no confidence that drugs manufactured in China are free from contamination and safe for Americans.
- 54% expressed the same concern about drugs manufactured in India.
- 94% favor giving FDA recall authority for drugs.

More specifically, the bill would:

- Give the FDA the authority to assess civil penalties for violations and to subpoena documents and witnesses.
- Facilitate exchange of information between the FDA and other regulatory agencies.
- Protect industry whistleblowers who bring information to the FDA.
- Require companies to institute quality management plans to ensure the quality and safety of their drugs and drug components, including strong supplier oversight.
- Require companies to document drug ingredient suppliers.
- Provide new oversight of over-the-counter (OTC) drugs and prevent the FDA "from relegating OTC drugs to a lower-risk category for site inspection simply because of their status."
- Require the FDA to establish a system that is interoperable, accurate, and has the ability to track all plants making drugs and active ingredients for the U.S. market.

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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	FDA's 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	FDA's Anesthetic and Life Support Drugs Advisory Committee
August 20	**Jazz Pharmaceuticals' Xyrem** (sodium oxybate, JZP-6) for fibromyalgia	FDA's 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	FDA's General and Plastic Surgery Devices Advisory Committee
September 2010		
September 7	**Forest/Cerexa's ceftaroline fosamil injection** for infection	FDA's Anti-Infective Drugs Advisory Committee
September 16	**Alkermes' Vivitrol** (naltrexone ER)	FDA's Psychopharmacologic Drugs Advisory Committee
September 16	**Arena Pharmaceuticals/Eisai's lorcaserin**, a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
September 16	**AstraZeneca's Brilinta** (ticagrelor)	PDUFA date
September 17 (not confirmed)	**Boehringer Ingelheim's Pradaxa** (dabigatran)	FDA's 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 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
October 2010		
October TBA	**Allergan's Botox** (onabotulinumtoxinA)	PDUFA date
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	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
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
Date TBA	**Abbott's Meridia** (sibutramine), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee to review the SCOUT trial data