Trends-in-Medicine

Quick Takes

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

SHORT TAKES

- **BIOGEN IDEC** licensed Knopp Neurosciences' dexpramipexole, which is being developed to treat amyotrophic lateral sclerosis (ALS). Biogen will lead development of the drug, which met its primary endpoint in a Phase II trial and already has orphan-drug status in the U.S. and Europe.
- **BIOMET's Signature Personalized Patient Care system –** The FDA issued a warning letter that this preoperative treatment plan system for Biomet's Vanguard knee does not have FDA clearance or approval. Biomet responded that it believes the product has 510(k) clearance and will resolve the issue with the FDA.
- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran) –** The FDA Cardiovascular and Renal Drugs Advisory Committee to considered Pradaxa was expected on September 17, 2010, and there is still a planned meeting of the panel on September 20, 2010, but there has been no announcement that Pradaxa is the topic.
- **BOSTON SCIENTIFIC** is discussing a sale of its neuromodulation business to **Stryker**. *The question is what Boston will do with the money – make an acquisition?*
- **BRISTOL-MYERS SQUIBB's ipilimumab** received priority-review status from the FDA as a treatment for advanced melanoma in previously-treated patients. The PDUFA date is December 25, 2010.
- **GLAXOSMITHKLINE's H1N1 vaccine** is being investigated by regulators in Sweden and Finland for possibly causing narcolepsy in children. Swedish authorities said six kids aged 12-16 developed narcolepsy 1-2 months after vaccination, and Finnish authorities also noted an increase in narcolepsy among children this spring.
- **Glioblastoma multiforme –** Researchers from the University of Massachusetts Medical School reported in ***Cancer Research***, a journal of the American Association for Cancer Research (AACR), that adding a Notch inhibitor to Merck's Temodar (temozolomide) was "dramatically" effective in reducing the recurrence of this aggressive brain cancer in mice and cell lines. The researchers called this proof-of-concept and hope to move the combination into clinical trials.

- **HUMAN GENOME SCIENCES/GLAXOSMITHKLINE'S Benlysta (belimumab)** has been granted priority review by the FDA. The PDUFA date is December 9, 2010.
- **IMMUNOGEN'S lorvotuzumab mertasine** was granted orphan-drug status by the FDA as a treatment for small-cell lung cancer. It already had orphan-drug status for Merkel cell carcinoma.
- **MEDCO HEALTH SOLUTIONS** is buying **United BioSource**, a research firm that helps clients (e.g., pharmas) determine the effectiveness and economic value of their products. United BioSource designs phone and web technologies for clinical trial patients to use to provide information about their health.
- **MEDTRONIC** is acquiring **Osteotech**, which is known for its demineralized bone matrix (DBM).
- **MELA SCIENCES' MelaFind –** The FDA advisory committee that was postponed has now been scheduled for November 18, 2010.
- **ROYAL PHILIPS ELECTRONICS** is participating in a new $250 million venture capital fund, Gilde Healthcare III, which will focus on early- and growth-stage healthcare technology companies in Europe and the U.S. In particular, the fund will be interested in home healthcare, sleep therapies, image-guidance interventions and therapies, and clinical decision support for cardiology, oncology, and women's health.
- **SANOFI-AVENTIS** is acquiring **TargeGen**, which is known for small-molecule kinase inhibitors for the treatment of leukemia, lymphoma, and other hematological malignancies and blood disorders. TargeGen's TG-101348 for myelofibrosis completed Phase I testing last year, and Phase II trials are expected to start this year.
- **Technetium-99 –** The end of the shortage could be in sight. The National Research Universal (NRU) reactor at Chalk River Laboratories in Canada – one of the world's largest producers of molybdenum-99 (Mo-99), the ore from which Technetium-99 is made – has been cleared by Canadian authorities to begin creating medical isotopes again after a 15 month shutdown.
- **XOMA** sold its royalty interest in the rheumatoid arthritis drug Cimzia (certolizumab pegol), which is marketed by **UCB Pharma**, for $4 million to an undisclosed buyer.

NEWS IN BRIEF

Acetaminophen
– associated with increased the risk of asthma in teens

A new study in the ***American Journal of Respiratory and Critical Care Medicine*** reported that 13- and 14-year-old children who take acetaminophen are more than twice as likely to have asthma as teens the same age who never took it.

The researchers studied 322,959 children, aged 13 to 14 years, at 113 centers in 50 countries, using written and video questionnaires about current symptoms of asthma, rhinoconjunctivitis, and eczema. The children also completed a written questionnaire about potential risk factors such as acetaminophen exposure in the preceding 12 months. The researchers noted that the study does ***not*** show that acetaminophen ***causes*** the problems.

Effect of Acetaminophen in Teens

Measurement	High use (≥ once a month)	Medium use (≥ once a year)
Acetaminophen use	30%	73%
Risk of asthma	2.5 times risk	Doubled
Rhinoconjunctivitis risk	Doubled	38% increase
Eczema risk	99% increase	31% increase

Cardiac stents
– cloud over the profession

The director of a Maryland cardiac cath lab has been accused of performing "hundreds, if not thousands, of unnecessary cardiac stent procedures on patients." Dr. Mark Midei of St. Joseph Medical Center in Towson MD is accused of medical fraud for putting stents in patients with "insignificant blockages." Dr. Midei has been an investigator for several drug-eluting stents and presented a poster at the American College of Cardiology in 2008, so he is not an obscure cardiologist.

The accusations are so serious that the Maryland Department of Health and Mental Hygiene was asked to investigate stenting procedures performed throughout Maryland during the past five years. *Will this give PCI a black eye? Will it expand to other states?*

European Society of Cardiology
– early released news

The embargo was lifted early on several interesting studies being presented at ESC, including:

- **Statins – be careful when switching brands.** A study conducted in the Netherlands using pharmacy data found that patients switching from a brand to a generic statin – specifically from Pfizer's Lipitor (atorvastatin) to simvastatin – often inadvertently got non-equivalent doses. The researchers found that in 1Q09, more than one-third of patients who had initially been prescribed Lipitor had been switched to a less potent dose of simvastatin. They concluded, "The predicted net effect of this would be at least a 5%-6% increase in LDL, which translates to a 3% average increase in the risk of heart disease and stroke."
- **Vitamin D – a prognostic marker in heart failure.** A Dutch study of 584 heart failure patients found that heart failure patients with low levels of vitamin D had a higher risk of death or re-hospitalization.

- **Statins – no cancer risk.** A meta-analysis of 25 trials with 170,000 patients found that statins do not increase the risk of cancer. The cancer rate was exactly the same in people taking statins as those taking placebo. There also was no increased risk with high-dose statins vs. standard-dose statins.
- **PCI vs. CABG – more risk stratification from SYNTAX trial.** A Dutch study found that incomplete revascularization in PCI patients with a high SYNTAX score markedly increased 5-year MACCE. Thus, they concluded that PCI patients with a high SYNTAX score should be offered surgery if stenting doesn't provide complete revascularization. Incomplete revascularization did not increase the risk vs. surgery for patients with a low or moderate SYNTAX score.
- **Proton pump inhibitors – increase cardiac risk when added to platelet inhibitors.** A meta-analysis of 160,000 patients by Austrian researchers found that patients who took both Sanofi-Aventis's Plavix (clopidogrel) and a PPI had a 29% increased risk of cardiovascular events and a 31% increased risk of MI – but no increased mortality risk. And the PPI decreased GI bleeding by 50%. The specific PPI used also made a difference, with, for example, more negative effects from omeprazole than panoprazole.

GLAXOSMITHKLINE's Avandia (rosiglitazone) – letter to doctors "biased"

FDA officials are not happy with a letter GSK sent about Avandia to doctors involved in the TIDE trial – comparing Avandia to Takeda's Actos (pioglitazone) – following the FDA Advisory Committee meeting on Avandia safety in July 2010. The FDA ordered GSK to send a letter to doctors describing the panel meeting, but some FDA officials and even some of the panel members called the July 28, 2010, letter misleading, saying it could endanger patients. Dr. David Graham, associate director for science and medicine in the FDA's Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research (CDER), called GSK's summary of the meeting, "biased, misleading, and not truthful." Panel member Dr. Clifford Rosen, a Maine endocrinologist, called the letter "deceptive," and panel member Dr. Curt Furberg of Wake Forest University described it as "very Avandia-friendly."

JAZZ PHARMACEUTICALS' JZP-6 (sodium oxybate) – rejected by FDA panel

The FDA's Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, meeting jointly, voted 20 to 2 to reject approval for JZP-6 as a treatment for fibromyalgia. The drug already has FDA approval, under the brand name Xyrem, to treat cataplexy (sudden loss of muscle control) and excessive daytime sleepiness in patients with narcolepsy. Panel members agreed with FDA reviewers that the drug is effective and safe, but concerns about the company's proposed risk management and evalution strategy (REMS), the proposed change in both name and concentration for fibromyalgia, and worries about whether the drug's availability would result in misuse and abuse turned the tide against approval.

The door is still open for approval, but Jazz likely will have to make several changes the panel suggested, including:

- Keep the Xyrem name.
- Keep the same dose/concentration.
- Improve the delivery system – perhaps making it child-proof, with individual doses, not large bottles of medicine.
- Use the existing REMS for Xyrem, but update it and make it even more restrictive.
- Possibly propose a postmarketing study.

Left ventricular assist devices (LVADs) – no Medicare reimbursement for Class IIIb patients

CMS issued a draft decision memo rejecting reimbursement for LVADs as destination therapy in Class IIIb patients, which Thoratec had requested. CMS is proposing reimbursement for Class IV destination therapy patients who meet specific criteria relating to prior medical management, LVEF, peak oxygen consumption, etc. However, body size is no longer a criteria. CMS decided that there are not enough data on Class IIIb patients and identifying Class IIIb patients would be difficult in clinical practice.

LILLY

➢ Cymbalta (duloxetine) – no clear guidance from FDA panel

The FDA's Anesthetic and Life Support Drugs Advisory Committee gave the FDA very weak guidance on what to do with Lilly's request to expand the indications for Cymbalta to include pain indications (musculoskeletal pain, which includes lower-back pain, and chronic pain). FDA officials told the panel that a broad chronic pain indication will not be granted.

After reviewing efficacy and safety data from three new Cymbalta studies in chronic low back pain and two new studies in chronic pain due to osteoarthritis of the knee, the panel voted:

- 8 to 6 **in favor of expanding approved use to include chronic musculoskeletal pain**.
- 8 to 5 (with 1 abstention) that Cymbalta **is effective in back pain**.
- 4 to 9 (with 1 abstention) that the evidence was convincing in osteoarthritis pain, thus saying there are **not enough data to support its use for OA pain**.

- That there are **not enough data to support a stronger 120 mg dose** over the current 60 mg dose.
- That the **overall safety profile is acceptable**.

➢ Semagacestat – development halted

All Alzheimer's disease trials of this gamma secretase inhibitor were stopped after preliminary results from two placebo-controlled trials of >2,600 patients not only failed to show any slowing of disease progression but also showed a worsening of cognition and the ability to perform the activities of daily living. Patients in the trials will no longer receive the drug, but they will be followed for at least six months.

The PET data, which may help researchers understand why semagacestat didn't work, will not be available for at least another six months. These results could have implications for other amyloid-targeting drugs in development.

Lilly is continuing development of solanezumab, a beta-amyloid inhibitor that is currently in Phase III.

Percutaneous aortic valves – monopolies are not good for patients

A study published in the ***Journal of the American College of Cardiology: Cardiovascular Interventions*** found that having both Edwards Lifesciences' Sapien and Medtronic's CoreValve valves available in a cath lab increases the number of patients who are suitable for a percutaneous valve. The Montreal Heart Institute researchers concluded, "This study of consecutive patients referred for TAVI demonstrates that with a two-device strategy, more patients are anatomically suitable for this therapy. The use of both devices is complementary and makes TAVI available for patients at either end of anatomical requirements."

In the study, the researchers evaluated 100 high-risk patients at two centers. They found a two-device strategy increased patient suitability by 9%, "With the combination of transfemoral devices available, the additional contribution of alternative access approaches (transapical for the Edwards Sapien system and transaxillary/direct aortic access for the Medtronic CoreValve system) is limited. We observed that 92% of cases were suitable for a multidevice transfemoral approach, and only 5% more cases were afforded treatment by the addition of other approaches. This supports the rationale that TAVI (transcatheter aortic valve implantation) should primarily be a catheterization laboratory-based transfemoral procedure, reserving other approaches for a minority."

Percutaneous Valve Suitability

Approach	Edwards	CoreValve
Transfemoral	28%	84%
Transapical	88%	---
Transaxillary/direct aortic	---	89%
Other	78% XT Novaflex	---
Unsuitable for procedure	12 patients (8 of these were suitable for CoreValve)	11 patients (8 of these were suitable for Sapien)
Unsuitable for both valves	3%	
Suitable for any procedure when both valves available	97%	97%

Most European hospitals offer only one valve or the other, largely because of the way the two companies have marketed their valves. Maybe this study will help change that.

ROCHE/GENENTECH's Herceptin (trastuzumab) – extends survival in gastric cancer

Herceptin extended median survival by 2.7 months (26%) in gastric cancer patients (13.8 months vs. 11.1 months for standard cisplatin/fluoropyrimidine chemotherapy). These findings came from a multicenter, international trial of 584 patients that was published in ***The Lancet***. However, an accompanying editorial questioned the cost-effectiveness, "In the 24 countries that contributed to the study, yearly health expenditure per citizen varies from $40 to $5,500, which reiterates the important moral question – what is the justification for introducing a treatment that might enable one individual to live a few months longer but will consume, for each person treated, the total yearly health expenditure for scores of their fellow citizens?"

FDA NEWS

FDA gets tough on accelerated approvals

It appears the FDA is getting tough with companies that get drugs approved under the accelerated approval process but fail to do the mandated postmarketing studies. The FDA started the process to withdraw approval of Shire's ProAmatine (midodrine hydrochloride) as well as generic midodrine (by Apotex, Impax Laboratories, and Mylan Pharmaceuticals) because the required postmarketing studies to verify the clinical benefit were never done.

ProAmatine received accelerated approval in 1996, and Shire was required to verify the clinical benefit with post-approval studies. However, neither Shire nor any generic manufacturer has ever done those studies to show that the drug improves a patient's ability to perform activities of daily living.

This is the first time the FDA ever issued a Proposal to Withdraw Marketing Approval and Notice of Opportunity for a Hearing to a company. Shire had 15 days to respond in writing if it wanted to request a hearing, but Shire said it will voluntarily withdraw ProAmatine on September 30, 2010.

Generic manufacturers will have 30 days to submit written comments. Then, if the FDA continues to believe withdrawal is warranted, approval of all midodrine products will be withdrawn.

Dr. Norman Stockbridge, director of the FDA's Division of Cardiovascular and Renal Drugs, CDER, said, "We've worked continuously with the drug companies to obtain additional data showing the drug's clinical benefits to patients. Since the companies have not been able to provide evidence to confirm the drug's benefit, the FDA is pursuing a withdrawal of the product."

The FDA estimates that ~100,000 U.S. patients filled midodrine prescriptions in 2009. The Agency is working with the manufacturers to develop an expanded-access program to allow patients who currently receive the drug to continue to get it on a case-by-case basis.

FDA extends lab test comment period

The FDA is reopening the comment period on laboratory-developed tests (LDTs) until September 15, 2010, to "update comments and to receive any new information." The original comment period ended August 15, 2010, but the FDA received a request for additional time to comment from an unidentified party who said the initial time period was insufficient.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest

(items in red are new since last week)

Date	Topic	Committee/Event
	August 2010	
August 26 Postponed until Nov. 18, 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 14	**Reauthorization of the medical device user fee program**	FDA public meeting
September 15	**Abbott's Meridia** (sibutramine), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
September 15	**Laboratory-developed test** (LDT) regulations	FDA extension for comments ends
September 16	**Alkermes' Vivitrol** (naltrexone ER) for opioid dependence	FDA's Psychopharmacologic Drugs Advisory Committee
September 16	**Arena Pharmaceuticals/Eisai's Lorqess** (lorcaserin), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
September 16	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
September 17	**Generic drug user fee program**	FDA public meeting
September 2010 **(possible but unlikely)**	**Boehringer Ingelheim's Pradaxa** (dabigatran), an anticoagulant	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
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 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 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
	December 2010	
December 7	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
December 9	**Human Genome Sciences/GSK's Benlysta** (belimumab) for lupus	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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