TRENDS-in-MEDICINE

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by Lynne Peterson

Quick Takes

…Highlights from this week's news relating to drugs and devices in development that are not covered in other *Trends-in-Medicine* reports…

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SHORT TAKES

- **AMGEN's Epogen (epoetin alfa) and Aranesp (darbepoetin alfa) –** Amgen reached a deal with **DaVita** to continue to provide at least 90% of the dialysis company's anemia drugs through 2018. *The question is how much DaVita use will decline under the new Medicare bundled payment system.*

- **APNEX MEDICAL's HGNS System –** A 30-patient study by Johns Hopkins researchers, published in the American Thoracic Society's ***Journal of Respiratory and Critical Care Medicine***, found that this implantable pacemaker-like device for hypoglossal nerve stimulation (HGNS) increased airflow during sleep in obstructive sleep apnea patients without waking them up. This would be an alternative to continuous positive airway pressure (CPAP) devices.

- **CELGENE's Revlimid (lenalidomide) –** At the recommendation of the data safety monitoring board, the company halted a Phase III trial of this multiple myeloma drug in prostate cancer, saying it failed to show more improvement in overall survival vs. chemotherapy (docetaxel) and steroids alone.

- **CELLDEX THERAPEUTICS' rindopepimut –** Phase II data presented at the Society for Neuro-Oncology meeting showed that this investigational brain cancer vaccine increased survival in patients with the EGFRvIII genetic mutation by an average of 9 months more than patients on standard therapy. A Phase III trial is expected to start later this year.

- **DENDREON's Provenge (sipuleucel-T) –** In June 2011 Medicare agreed to cover the $93,000 cost of this immunotherapy for prostate cancer, and now Medicare has agreed to reimburse doctors for the cost of administering the treatment as well – and it will retroactively pay doctors back to June 30.

- **Drug-eluting stents (DES) –** The FDA is investigating rare cases of DES longitudinal compression "to better understand longitudinal stent deformation with respect to its causes, predisposing underlying anatomic conditions, operator techniques that can reduce the likelihood of its occurrence, and treatment strategies should it occur."

- **EXELIXIS' cabozantinib –** The company announced that an open-label, single-arm, 50-patient, multicenter, 12-week, investigator-initiated Phase II trial has begun in women with hormone receptor-positive breast cancer that has metastasized to the bone. The primary endpoint is bone scan response rate determined by local institutions and by an independent radiology facility.

- **GILEAD SCIENCES** is spending $11 billion to buy **Pharmasset**, which has an all-oral therapy (without pegylated interferon) for hepatitis C in Phase III development.

- **GLAXOSMITHKLINE's Avandia (rosiglitazone)** – The FDA rejected Public Citizen's 2008 petition to have Avandia banned. Public Citizen estimates that ~1.1 million prescriptions were written for Avandia-containing drugs in the U.S. in the last year. Sidney Wolfe, MD, director of Public Citizen's Health Research Group, called the FDA's decision not to ban the drug but to limit prescriptions "a dangerous and reckless refutation of the precautionary principle that is supposed to guide decisions involving public health."

- **JOHNSON & JOHNSON's Doxil (doxorubicin liposomal)** – Ben Venue Laboratories, the contract manufacturer for this cancer medication, ceased production and will no longer distribute Doxil from its Ohio plant because preventive maintenance and requalification of other maintenance equipment are overdue.

- **LILLY's LY-2886721** – Lilly may have found a follow-on compound that solves the ocular toxicity problems that killed its oral BACE1 inhibitor, LY-2811376, for Alzheimer's disease before it even got to Phase II. Three Phase I trials of LY-2886721 are under way. According to an article in ***Alzheimer Research Forum***, this would be the first orally available CNS-active β-secretase inhibitor after more than a decade of research.

- **Mammography** – Canadian mammography guidelines were revised and now recommend that women age 50-74 get a mammography every 2-3 years (not annually) and that women age 40-49 not be routinely screened at all.

- **MEDICIS PHARMACEUTICAL** won a bankruptcy auction for **Graceway Pharmaceuticals**, which made skin treatments and asthma medications, but Medicis still needs the approval of Graceway's board of directors and the Delaware bankruptcy court.

- **MYLAND** was warned by the FDA about "significant" manufacturing violations at its Puerto Rican plant. *Haven't all the companies had problems with their Puerto Rican manufacturing?*

- **OTSUKA and LUNDBECK's once-monthly aripiprazole** depot formulation is under review by the FDA.

- **PEREGRINE PHARMACEUTICALS' bavituximab** – Adding this antibody to standard chemotherapy in a Phase II trial increased survival by 7 months in patients with locally advanced metastatic breast cancer vs. standard chemotherapy alone.

- **PFIZER** is buying privately held **Excaliard Pharmaceuticals**, which has EXC-001, a treatment to reduce skin scarring or fibrosis, in Phase II development.

- **REGENERON PHARMACEUTICALS' Arcalyst (rilonacept)** was accepted by the FDA for review to treat gout. It already is approved to treat cryopyrin-associated periodic syndromes (CAPS).

- **SHIRE's Vpriv (velaglucerase alfa)** – The company filed applications with both the FDA and the European Medicines Agency (EMA) to produce this Gaucher disease drug at a new manufacturing site in Massachusetts.

- **SPECTRUM PHARMACEUTICALS' Zevalin (ibritumomab tiuxetan)** – The FDA removed a requirement that patients undergo a scan during treatment with this non-Hodgkin's lymphoma drug, making it easier for both patients and physicians.

NEWS IN BRIEF

JOHNSON & JOHNSON/ETHICON ENDO-SURGERY's Sedasys – FDA advisory panel to hear appeal

The FDA will hold an advisory committee meeting on J&J's appeal of its negative decision on this computer-assisted personalized sedation system for administering IV propofol to adult patients undergoing colonoscopy or esophagogastroduodenoscopy (EGD) procedures.

In May 2009, the FDA's Anesthesiology and Respiratory Therapy Devices Advisory Committee voted 8-2 that the device was "approvable with conditions." However, in February 2010, the Centers for Devices and Radiological Health (CDRH) rejected Sedasys, saying it was not approvable because "the data and information offered in support of the PMA did not provide a reasonable assurance that the device is safe."

In March 2010, J&J petitioned the FDA for a reconsideration of the not-approvable letter, and this nine-member advisory committee meeting is tasked with reviewing the decision publicly and making a report to the FDA Commissioner.

The two key issues are:

- CDRH's opinion that Sedasys is associated with an increased incidence of deeper-than-intended sedation in the pivotal trial and that this poses a serious safety signal. CDRH also does not believe the company's proposed training program is adequate.
- The adequacy and appropriateness of the control arm used by J&J in the pivotal trial, which was a non-blinded comparison.

The FDA's draft questions for the panel are:

1. Do the incidents of deeper-than-intended sedation observed in the Sedasys pivotal trial, including general anesthesia in five patients in the Sedasys group compared to one patient in the control group, represent a clinically significant safety concern?
2. Do any probable benefits to health from use of Sedasys outweigh any probable risks?
3. Was the clinical trial comparing propofol administration by gastroenterology teams via Sedasys with administration of benzodiazepine/opioid combinations by gastroenterology teams appropriate to determine whether there is a reasonable assurance that the device is safe for its proposed intended use?
4. Should a clinical trial instead compare administration of propofol by gastroenterology teams via Sedasys with administration of propofol without the device by persons trained in the administration of general anesthesia?
5. Does the PMA demonstrate that the training the company proposed for the intended user group adequately addresses the risk of incidents of deeper-than-intended sedation, including the incidents of general anesthesia seen in the pivotal trial, and the possible consequences of these events?
6. Does the training program need to be validated to ensure that it adequately mitigates such risks, and, if so, how could this be done?

MERZ

- **Belotero.** This facial filler was approved by the FDA. Merz acquired **Radiesse** in 2010 with the purchase of **BioForm**.
- **Xeomin (incobotulinumtoxinA).** This toxin was approved for cosmetic purposes by the FDA in July 2011, and the company is just starting to ship it, at least in limited quantities, with full U.S. availability not expected until 2012. It is priced ~20% less than **Allergan's Botox** (onabotulinumtoxinA) and just slightly less than **Medicis' Dysport** (abobotulinumtoxinA).

TAKEDA PHARMACEUTICAL

- **Alogliptin.** The FDA delayed review of this DPP-4 diabetes drug (which is marketed in Japan as Nesina), saying it needed more time to review the data. The new PDUFA date is April 25, 2012.
- **Dexilant (dexlansoprazole).** The FDA updated the label to say that this proton pump inhibitor (PPI) ***is*** compatible with **Sanofi's Plavix** (clopidogrel).

TRANSCEPT PHARMACEUTICALS' Intermezzo (zolpidem tartrate sublingual tablets) – first middle-of-the-night insomnia drug

Intermezzo was approved by the FDA for use as needed to treat insomnia characterized by middle-of-the-night awakening followed by difficulty returning to sleep. This is the first drug approved for this indication, and different maximum doses were approved for men (3.5 mg) and women (1.75 mg). **Pfizer's Ambien** (zolpidem) was approved in 1992 at a maximum dose of 10 mg, but with the same dose for men and women. Generic zolpidem was approved in 2007.

REGULATORY NEWS

Bill to block regulation of genetic tests

Rep. Michael Burgess (R-TX), who is a physician, introduced legislation that would block the FDA from regulating genetic tests.

CMS gets a new leader

CMS administrator Donald Berwick, MD, hasn't been confirmed by the U.S. Senate, and probably won't before the end-of-the-year deadline, so he and the White House are giving up. Dr. Berwick will step down on December 2, 2011, and will be replaced by his deputy, Marilyn Tavenner, who is a nurse. She formerly was secretary of Virginia's Health and Human Services Department. She spent 25 years with Hospital Corporation of America (HCA), starting as a nurse and eventually becoming president of outpatient services.

Well-known Dutch cardiologist fired, prompting practice guidelines review

Erasmus Medical Center fired Don Poldermans, MD, PhD, a well-known cardiologist and researcher, for violations of academic integrity, saying he "used patient data without written permission…used fictitious data, and that two reports were submitted to conferences that included knowingly unreliable data."

As a result, Dr. Poldermans resigned from the European Society of Cardiology's Committee for Practice Guidelines, and the ESC is reviewing whether some of their guidelines need to be re-examined in light of his role in their creation, in particular the "Guidelines for preoperative cardiac risk assessment and preoperative cardiac management in non-cardiac surgery," which Dr. Poldermans chaired.

FDA warns manufacturers/distributors about unapproved fluorescein dye

The FDA sent warning letters to manufacturers and distributors of unapproved **Fluorescein Injection** – a dye injected into the vein for evaluation of eye conditions – to cease production and distribution of unapproved products. There are FDA-approved versions of this drug on the market for use in diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature, and the FDA will no longer allow unapproved products.

- **Altaire Pharmaceuticals** was given 90 days to stop manufacturing its unapproved drug.
- **Hub Pharmaceuticals** was given 180 days to stop distributing unapproved drugs.

The FDA-approved Fluorescein Injection products are: **Alcon's Fluorescite 10%**, and **Akorn AK-Fluor 10% and 25%**. The FDA said these two companies have the capacity to supply the market's needs.

FDA approvals/clearances

- **APTUS ENDOSYSTEMS' Aptus EndoStapling System**, a less-invasive system for repairing fixed aortic aneurysms endografts (repairs) than open surgery. It was approved through the de novo reclassification process based on a review of data from 154 patients implanted with 810 EndoStaples monitored for a year without any of them migrating or fracturing. However, the company is changing the name to **HeliFX Aortic Securement System**.
- **BOSTON SCIENTIFIC's Promus Element Plus** platinum-chromium drug-eluting stent.
- **BSD MEDICAL's BSD-2000** hyperthermia device, which is used in combination with radiation therapy to treat patients with cervical cancer who are not able to undergo chemotherapy, was granted a humanitarian device exemption (HDE).
- **MEDTRONIC's iPro2** continuous glucose monitoring system.

European regulatory actions

- **ASTRAZENECA's Caprelsa (vandetanib)** received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) to treat advanced medullary thyroid cancer, and it will now be reviewed by the European Commission. It is already approved by the FDA.
- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran)** – There are now 256 known cases of fatal bleeding with this stroke-prevention drug for atrial fibrillation patients, and the EMA urged doctors to use caution when prescribing it. The EMA also said lower doses need to be used in patients age >75 to adequately manage the bleeding risk.
- **OTSUKA's Busilvex (busulfan)** – The EMA recalled this cancer drug due to concern with the sterilization process at the U.S. plant making it.
- **TAKEDA's Velcade (bortezomib)** – The EMA recalled this cancer drug due to concern with the sterilization process at the U.S. plant making it.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	December 2011	
December tba	**Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to be completed	Company announcement or medical conference presentation
December 1	Review of **risk evaluation and mitigation strategies** (REMS), including iPLEDGE for isotretinoin	FDA's Drug Safety and Risk Management Dermatologic and Ophthalmic Drugs Advisory Committees meeting jointly
December 5	Using scientific research data to support a **pediatric medical device claim**	FDA public workshop
December 7	**Pfizer's Inlyta** (axitinib) for advanced renal cell carcinoma and **Affymax's peginesatide injection** for anemia in chroic renal failure dialysis patients	FDA's Oncologic Drugs Advisory Committee (ODAC)
December 7	Expanding the indication for **Medtronic's CRT-D devices** to symptomatic NYHA Class II patients with LBBB, QRS ≥120 ms, and LVEF ≤30%	FDA's Circulatory System Devices Advisory Committee
December 8	**CardioMEMS' CardioMEMS HF Pressure Measurement System**, a permanently implantable pulmonary arterial pressure measurement system	FDA's Circulatory System Devices Advisory Committee
December 8	**Antares Pharma's Anturol** (transdermal oxybutynin ATD gel), for OAB	PDUFA date
December 8	**Bayer's Yaz, Yasmin, and Beyaz** (drospirenone) blood clot safety review	FDA's Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committees meeting jointly
December 9	**Johnson & Johnson/Janssen's Ortho Evra** (norelgestromin/ethinyl estradiol transdermal system) blood clot safety review	FDA's Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committees meeting jointly
December 12	**Alexza Pharmaceuticals' Adasuve** (loxapine inhalation powder) for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. Pulmonary safety is the key concern.	FDA's Psychopharmacologic Drugs Advisory Committee
December 13	**Endo Pharmaceuticals' Opana** (extended-release oxymorphone) for pain	PDUFA date
	January 2012	
January	**Pfizer's Prevnar 13** (PCV13), a pneumococcal vaccine for adults	PDUFA date
January 3	**Medical device labeling** feedback is sought	FDA deadline for public comment
January 11	**Torax Medical's LINX Reflux Management System** to treat the symptoms associated with gastroesophageal reflux disease (GERD)	FDA's Gastroenterology and Urology Devices Advisory Committee
January 20	Efficacy of **Columbia Laboratories' progesterone gel 8%** to reduce the risk of preterm birth in women with short uterine cervical length	FDA's Reproductive Health Drugs Advisory Committee
January 28	**Bristol-Myers Squibb and AstraZeneca's dapagliflozin**, a first-in-class SGLT2 inhibitor for Type 2 diabetes	PDUFA date
January 28	**Eli Lilly, Amylin Pharmaceuticals and Alkermes' Bydureon** (weekly exenatide XR), an injectable drug for Type 2 diabetes	FDA decision date
	February 2012	
February	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation
February 4	**Alexza Pharmaceuticals' Adasuve** (loxapine inhalation powder) for the acute treatment of agitation associated with schizophrenia/bipolar I disorder	PDUFA date
February 10	Possible reclassification of **cranial electrotherapy stimulator (CES) devices** to Class III (requiring a PMA)	FDA's Neurological Devices Advisory Committee
February 17	**Corcept Therapeutics' Corlux** (mifepristone) for Cushing's syndrome	PDUFA date
February 27	Review of evidence needed for approval of **anti-inflammatory ophthalmic drugs post-ocular surgery** and appropriateness of marketing a single bottle for use in both eyes post-surgery	FDA's Dermatologic and Ophthalmic Drugs Advisory Committee
February 28	**Pfizer's axitinib** for advanced renal cell carcinoma	PDUFA date (*approximate*)
	March 2012	
March tba	**Anti-nerve growth factor (NGF)** drug class safety review	FDA's Arthritis Advisory Committee – originally scheduled for September 13, 2011, but postponed indefinitely, now March 2012
March 6	**Discovery Labs' Surfaxin** (lucinactant) for infant respiratory disease	PDUFA date
March 7	**NeurogesX' Quetenza** (transdermal capsaicin) for HIV-related neuropathic pain)	PDUFA date
March 8	**Roche/Genentech and Curis' vismodegib,** a Hedgehog pathway inhibitor for advanced basal cell carcinoma in adults for whom surgery is not an option	PDUFA date
March 27	**Affymax and Takeda's peginesatide** for anemia	PDUFA date
March 28	**Chelsea Therapeutics' Northera** (droxidopa) for symptomatic neurogenic orthostatic hypotension with primary autonomic failure	PDUFA date
March 28	**Edwards Lifesciences' Sapien** transcatheter aortic valve	CMS expected to publish NCD decision memo

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	April 2012	
April 17	**Vivus' Qnexa** (phentermine + topiramate) for weight loss	PDUFA date for resubmission
April 25	**Takeda's alogliptin,** a DPP-4 for Type 2 diabetes	***New*** PDUFA date
April 26	**Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in prostate cancer	PDUFA date
April 27	**Salix Pharmaceuticals and Progenics Pharmaceuticals' Relistor** (methylnaltrexone injection) for opioid-induced constipation	PDUFA date
April 29	**Vivus' avanafil** for erectile dysfunction	PDUFA date
April 30	**Baxter and Halozyme's HyQ** for immunodeficiency	PDUFA date
	Other 2012	
June	**Forest Laboratories and Ironwood Pharmaceuticals' linaclotide** for IBS-C	PDUFA date
June 25	**QRxPharma's MoxDuo** (morphine + oxycodone)	PDUFA date
June 26	**Edwards Lifesciences' Sapien** transcatheter aortic valve	CMS final NCD expected
July 30	**Regeneron's Arcalyst** (rilonacept) for gout	PDUFA date
August	**Pfizer's tofacitinib,** an oral JAK2 inhibitor for rheumatoid arthritis	PDUFA date