TRENDS-in-MEDICINE

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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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NOTE: Subscribe to ***Trends-in-Medicine*** for full coverage of the American Diabetes Association (ADA) meeting.

SHORT TAKES

- **AMYLIN PHARMACEUTICALS and ALKERMES' Bydureon (exenatide extended-release) –** The FDA wants more data before approving a new pen-delivery system for this once-weekly injectable GLP-1 receptor agonist for Type 2 diabetes, which means it is unlikely to be available before 2013 at the earliest.

- **AUXILIUM PHARMACEUTICALS' Xiaflex (collagenase clostridium histolyticum) –** Two Phase III trials showed that this injectable drug is effective in treating Peyronie's disease (a curvature of the penis).

- **CEPTARIS THERAPEUTICS' mechlorethamine gel –** The FDA rejected this drug to treat early-stage mycosis fungoides, a type of cutaneous T-cell lymphoma (CTCL), issuing a complete response letter.

- **COOPER COMPANIES** is acquiring Denmark-based **Origio**, the No. 1 player in the *in vitro* fertilization market.

- **DR. REDDY'S LABORATORIES** and **Merck KGaA/Serono** have agreed to co-develop biosimilar medications for sale in the U.S., Europe, and Japan, focusing on cancer medications.

- **Electronic health records (EHRs) –** The rate of registration by physicians and other "eligible professionals" for Medicare and Medicaid incentive payment programs for use of EHRs fell for the second straight month in April, down 12% from March. Currently, there are almost 200,000 physicians and 3,569 hospitals registered.

- **INSIGHT IMAGING** and the **Center for Diagnostic Imaging (CDI)**, two of the nation's largest medical imaging companies, are merging.

- **JOHNSON & JOHNSON/ETHICON** plans to stop selling four of its five vaginal mesh implants – **Prolift, Prolift+ M, TVT Secur,** and **Prosima** – after being sued by >600 women who claim the products caused internal injuries. Only **Gynecare Gynemesh** will remain on the market, though the company is asking for a more restrictive label. J&J also asked the FDA for a 120-day transition period before ending sales, so customers have time to find alternatives. J&J emphasized that this is not a recall, just that the products are no longer commercially viable.

- **Medical device tax –** The House of Representatives voted 270-146 to repeal the 2.3% tax on makers of medical devices that is part of the Affordable Care Act. The

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repeal has little chance in the Senate, and even if it did, President Obama has threatened to veto it.

- **NEKTAR THERAPEUTICS' NKTR-181 –** The FDA granted fast track status to this drug for moderate-to-severe chronic pain. The company plans a rolling submission.

- **NOVO NORDISK's Degludec and DegludecPlus (recombinant human basal insulin) –** The FDA extended its review time for these two ultralong-acting basal insulin analogs in order to review additional data provided by the company that the FDA considers a "major amendment." No new clinical trials have been requested by the Agency. The new PDUFA date is October 29, 2012.

- **ONYX PHARMACEUTICALS** and the University of Texas MD Anderson Cancer Center signed a non-exclusive research alliance for pre-clinical and clinical research on investigational drugs, including Onyx's carfilzomib and oprozomib for multiple myeloma and lymphoma.

- **OTSUKA PHARMACEUTICAL's delamanid –** A study published in the ***New England Journal of Medicine*** found that this investigational antibiotic cleared multidrug-resistant tuberculosis bacteria from lung fluid in almost half the patients, a much better response than produced by older anti-TB medications. In an accompanying editorial, two Johns Hopkins researchers urged the company to speed up development of what could become the first new drug for TB in 40 years.

- **QUESTCOR PHARMACEUTICALS' Acthar (adrenocorticotropic hormone, ACTH, gel) –** A single-center, retrospective, 18-patient study presented at the joint meeting of the Consortium of Multiple Sclerosis Centers (CMSC) and the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) found this injectable drug is an effective treatment for MS exacerbations in patients failing methylprednisolone therapy. However, the researcher noted that the drug's cost (~$30,000 for a 5-day course) and lack of reimbursement limit its use.

- **SANOFI's Aubagio (teriflunomide) –** This oral drug for multiple sclerosis missed the primary endpoint in a 324-patient Phase III, failing to show superiority to **Merck/Serono's Rebif** (interferon beta-1a), an injectable therapy, on either relapses or drug discontinuation. The two drugs looked very similar, but the trial was designed as a superiority study, not a non-inferiority trial. Permanent discontinuations were substantially less common with teriflunomide, but relapses were more common.

- **SMITH & NEPHEW –** The company is pulling its metal hip socket liner for the **R3 Acetabular System** off the market, saying it is "not satisfied with the clinical results of this component." The revision rate with the device was 1.6%, and the rate considered acceptable in the U.K. is 1%. The company said 7,700 of the liners have been implanted since 2009.

- **VERTEX PHARMACEUTICALS' Kalydeco (ivacaftor) + VX-809 –** Sen. Charles Grassley (R-IA) asked the Securities and Exchange Commission to investigate whether Vertex executives sold shares of the company's stock illegally in the window between the original results for this cystic fibrosis combination therapy and a revision in the results three weeks later.

NEWS IN BRIEF

MERCK

- **MK-3102** (for diabetes) and **MK-5172** (for hepatitis C). A Chinese scientist was convicted in a Shanghai court of stealing and selling these patented drugs. *So, maybe China is cracking down a bit on patent theft.*

- **Suvorexant.** The company announced that data from a Phase III trial indicated that this insomnia medication is effective long term (12 months). This is reportedly the only insomnia drug ever tested for a full year. Merck plans to submit suvorexant to the FDA this year.

- **Taltorvic (ridaforolimus).** The FDA rejected this investigational drug for metastatic soft-tissue or bone sarcoma (which is being co-developed with Ariad Pharmaceuticals), saying another human safety and efficacy study is needed. The FDA's Oncologic Drugs Advisory Committee (ODAC) previously voted 13-1 that this mTOR inhibitor should not be approved because of a short improvement in PFS, no improvement in overall survival, and significant side effects.

ROCHE/GENENTECH

- **Actemra (tocilizumab).** In a head-to-head study in rheumatoid arthritis (RA), presented at the European League Against Rheumatism (EULAR) meeting in Berlin, this immunosuppressant beat **Abbott's Humira** (adalimumab), showing a greater ability to reduce tender and swollen joints and other measures in RA patients who couldn't take methotrexate.

- **Erivedge (vismodegib, GDC-0449).** A Phase III study published in the ***New England Journal of Medicine*** found that this hedgehog inhibitor, which is approved to treat large

basal cell carcinoma and made in collaboration with **Curis**, also appears effective against basal cell nevus syndrome, a rare, disfiguring skin cancer.

Spinal injuries – progress in reversing paralysis

A rat study by Swiss researchers, published in ***Science***, found that combining neurotransmitter (serotonin and dopamine receptor agonists) injections, electrical stimulation of the spinal cord, and physical therapy with a robotic support system could restore ***voluntary*** movement in injured animals. The study showed that – with the right encouragement (in this case a chocolate treat) – the spinal cord can be plastic enough to piece together new neural pathways that bypass damaged ones.

Whether this will work in humans is unknown, but it would only apply to patients with some spinal cord connections, which is about a third of paralyzed patients. The researchers implanted a stimulating electrode array in the spinal dura of a 23-year-old paraplegic, and after 80 training sessions he was able to stand for more than four minutes and control limb movements.

REGULATORY NEWS

FDA reports of serious/fatal drug reactions in 2011

According to QuarterWatch, an Institute for Safe Medication Practices surveillance program that monitors all serious and fatal adverse drug events reported to the FDA through MedWatch, the FDA received 179,855 reports of serious or fatal adverse drug reactions last year, up 9.4% from 2010. Only three of the top 10 drugs with the most reports were new drugs:

- **Boehringer Ingelheim's Pradaxa (dabigatran)** was No. 1, with 3,781 reports, 542 deaths, 2,367 hemorrhages, 291 acute renal failures, 644 strokes, and 15 cases of suspected liver failure.
- **Coumadin (warfarin)**
- **Johnson & Johnson's Levaquin (levofloxacin)**
- **Carboplatin**
- **AstraZeneca's Zestril (lisinopril)**
- **Cisplatin**
- **Merck's Zocor (simvastatin)**
- **Lilly's Cymbalta (duloxetine)**
- **Bayer's Cipro (ciprofloxacin)**
- **Mutual Pharmaceutical's Bactrim (trimethoprim and sulfamethoxazole)**

FDA medical device dispute-handling criticized

The Office of the Inspector General (OIG) of the Department of Health and Human Services (HSS) issued a report recommending that the FDA better define the way it documents and resolves scientific disagreements between medical-device reviewers and managers. The OIG also said the FDA should train reviewers and managers on new policies and procedures for resolving scientific disagreements and "more clearly assign accountability for the contents of the administrative files of all submissions." The FDA agreed with the recommendations.

According to the report, there were 36 internal scientific disagreements at the FDA's Center for Devices and Radiological Health (CDRH) from FY2008 to FY2010, most commonly over 510(k) submissions. The FDA strengthened dispute procedures in 2009, but ~50% of the reviewers and ~25% of the managers said they had not been trained in the new procedures.

FDA approvals/clearances

- **CALGARY SCIENTIFIC's ResolutionMD Web 2.9** vessel analysis module was cleared for use to help users perform post-processing diagnostic analysis of MRI and CT scans and report vascular anatomy data across specialties.
- **HANSEN MEDICAL's Magellan Robotic System**, which helps surgeons perform peripheral vascular interventions, was granted 510(k) clearance. The company plans to launch it immediately at a limited number of U.S. facilities, with a full commercial release later this year.
- **MELICOR MEDICAL's Laparoscopic Lens Internal Cleaning System (LLICS)** – The FDA approved this device, an inexpensive and disposable method of cleaning the lenses of devices used by surgeons in minimally-invasive laparoscopic procedures.
- **ROCHE/GENENTECH's Perjeta (pertuzumab)** – The FDA approved this targeted antibody to treat HER2+ breast cancer – in combination with Herceptin (trastuzumab) and Sanofi's Taxotere (docetaxel) – in women who haven't received prior treatment for the disease.
- **SOLOHEALTH's SoloHealth Station**, a health and wellness screening kiosk for consumers, was approved. It is already in some U.S. test markets and retail locations, and the company plans to put thousands of the kiosks in retail pharmacies around the country by end of 2012. The free kiosks provide health screenings for vision, blood pressure, weight, and body mass index.

- **XENOPORT and GLAXOSMITHKLINE's Horizant (gabapentin enacarbil)** – The FDA granted an additional indication for this restless leg drug – the treatment of post-herpetic neuralgia.

FDA recalls/warnings

- **NOVARTIS/SANDOZ's Introvale (levonorgestrel and ethinyl estradiol)** – Sandoz initiated a voluntary, precautionary recall of these birth control pills because of a packaging error.
- **SAL PHARMA and PAN DRUGS** – Both of these Indian drug companies were warned by the FDA that they have failed to adequately correct non-compliance with registration law. Continued failure could lead to severe action by the FDA, including a ban on sales in the U.S.
- **SIEMENS' AD VIA Centaur iPTH immunoassay** – The FDA sent a warning letter to Siemens Healthcare Diagnostics that this assay does not comply with current good manufacturing practice requirements and does not have the proper PMA approval. There was also a lesson for other pharmas and device companies in the letter. Don't expect the FDA to go to a website to retrieve information it requests; send it directly. The FDA clearly didn't like Siemens' initial email response to the manufacturing site inspection, writing, "The email did not provide attachments related to your response. However, the email indicated a signed response as well as attachments were available for the FDA by logging onto a Siemens File Exchange. The District did not and does not plan to logon to your firm's File Exchange to obtain responses or other information."

European regulatory actions

- **NEURONETICS' Neurostar TMS Therapy** system, which uses transcranial magnetic stimulation to treat depressive disorders, was granted a CE Mark.
- **NINEPOINT MEDICAL's NVision VLE Imaging System**, an optical endomicroscopy imaging device used to detect mucosa and submucosa conditions, was granted a CE Mark.
- **ORTHO CLINICAL DIAGNOSTICS' Vitros 25-OH Vitamin D Total Assay** was granted a CE Mark.
- **VIVUS' Qnexa (phentermine + topiramate)** – The European Medicines Agency (EMA) gave the company extra time to prepare for an oral hearing on this investigational diet drug in September 2012.

Regulatory news from other countries

Japan:

- **ASTRAZENECA**
  - **Oxis (formoterol)** was approved to treat chronic obstructive pulmonary disease (COPD).
  - **Symbicort (budesonide + formoterol)** was approved to treat bronchial asthma.
- **PFIZER**
  - **Zithromax (azithromycin)** was approved to treat pelvic inflammatory disease.
  - **Inlyta (axitinib)** was approved to treat metastatic or inoperable renal cell carcinoma.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	June 2012	
June 13	**Edwards Lifesciences' Sapien** transcatheter aortic valve repair (TAVR), an expanded indication for high-risk, operable patients	FDA's Circulatory System Devices Advisory Committee
June 15	**Gilead Sciences' Truvada** (emtricitabine + tenofovir) for HIV prevention	PDUFA date
June 20	**Onyx Pharmaceuticals' carfilzomib**, a treatment for relapsed and refractory multiple myeloma	FDA's Oncologic Drugs Advisory Committee (ODAC)
June 21	**Dune Medical Devices' MarginProbe System**, which uses electromagnetic waves to characterize human tissue and provides intraoperative information on a malignancy of the surface of *ex vivo* lumpectomy specimens	FDA's General and Plastic Surgery Devices Advisory Committee
June 21	**Repligen's RG-1068**, an imaging agent to help identify abnormalities in pancreatic ducts	PDUFA date
June 25	**QRxPharma's MoxDuo** (morphine + oxycodone) for pain	PDUFA date
June 27	**Arena Pharmaceuticals and Eisai's Lorqess** (lorcaserin) for obesity	PDUFA date
June 27	**Onyx Pharmaceuticals' carfilzomib**, a treatment for relapsed and refractory multiple myeloma	PDUFA date
June 27-28	Risk:benefit of **metal-on-metal hip replacement** and **resurfacing**	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
June 28	**Bristol-Myers Squibb's Eliquis** (apixaban), an anticoagulant for the prevention of stroke in Afib	PDUFA date
June 29	**Johnson & Johnson's Xarelto** (rivaroxaban) for acute coronary syndrome	PDUFA date
June 29	**Astellas Pharma's Betanis** (mirabegron) to treat overactive bladder	PDUFA date
	July 2012	
July 17	**Vivus' Qnexa** (phentermine + topiramate) for weight loss	PDUFA date (extended from April 17)
July 24	**GlaxoSmithKline's Tykerb** (lapatinib) **+ Roche's Herceptin** (trastuzumab), supplemental indication for HER2+ metastatic breast cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
July 25	Discussion of presurgical identification of clear-cell carcinoma of the kidney using an imaging test	FDA's Oncologic Drugs Advisory Committee (ODAC)
July 26	**Amarin's AMR-101** (omega-3 fish oil EPA) to treat hypertriglyceridemia	PDUFA date
July 26	**Horizon Pharma's Lodotra** (low-dose prednisone) for rheumatoid arthritis	PDUFA date
July 27	**Onyx Pharmaceuticals' carfilzomib** for multiple myeloma	PDUFA date
July 27	**Salix Pharmaceuticals and Progenics Pharmaceuticals' Relistor** (subcutaneous methylnaltrexone bromide) for chronic non-cancer pain	PDUFA date
July 30	**Regeneron's Arcalyst** (rilonacept) for gout	PDUFA date
July 30	**Almirall and Forest Laboratories' aclidinium** inhaled therapy for chronic obstructive pulmonary disease (COPD)	PDUFA date
	August 2012	
August 4	**Regeneron Pharmaceuticals** and **Sanofi's Zaltrap** (aflibercept) for colon cancer	PDUFA date
August 12	**Talon Therapeutics' Marqibo** (vincristine sulfate liposomes injection) for Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL)	PDUFA date (extended from May 13)
August 21	**Pfizer's tofacitinib**, an oral JAK2 inhibitor for rheumatoid arthritis	PDUFA date
August 27	**Gilead Sciences' Quad** (emtricitabine+tenofovir+elvitegravir+cobicistat) for HIV	PDUFA date

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
Other 2012		
September tba	**Vivus' Qnexa** (topiramate + phentermine) for obesity	EMA oral hearing
September 5	**Salix Pharmaceuticals' Provir** (crofelemer) for HIV-related diarrhea	PDUFA date (extended from June 5)
September 8	**Ironwood Pharmaceuticals and Forest Laboratories' linaclotide** for irritable bowel syndrome	PDUFA date
September 10	**Navidea Biopharmaceuticals' Lymphoseek**, a radioactive agent for tracing lymph nodes in cancer patients	PDUFA date (extended from June 10)
September 23	**Regeneron's Eylea** (aflibercept) for central retinal vein occlusion (CRVO)	PDUFA date
October 21	**Impax Laboratories' IPX-066** for Parkinson's disease	PDUFA date
October 29	**Cornerstone Therapeutics' CRTX-080** to treat hyponatremia	PDUFA date
October 29	**Novo Nordisk's Degludec and DegludecPlus** (human recombinant basal insulin)	***New*** PDUFA date (extended from July 29)
2013		
January 29	**Sanofi/Genzyme and Isis Pharmaceuticals' Kynamro** (mipromersen) for homozygous familiar hypercholesterolemia	PDUFA date