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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SHORT TAKES

- **ALEXZA PHARMACEUTICALS' Adasuve (loxapine) –** The company said the FDA accepted its resubmitted new drug application (NDA) for this drug to treat agitation associated with schizophrenia or bipolar disorder.

- **BIOGEN IDEC** and **ISIS PHARMACEUTICALS** are collaborating to develop an antisense drug to treat myotonic dystrophy, a debilitating neuromuscular disease also known as Steinert disease.

- **Cystatin C –** A study published in the ***New England Journal of Medicine*** found that cystatin C levels – along with serum creatinine – are better at assessing kidney impairment than the standard glomerular filtration rate (GFR) formula. The researchers found substantially more patients were ***correctly*** classified as having GFR values above or below the 60 ml/min/1.73 m^2 threshold when GFR was figured along with cystatin levels v. serum creatinine alone.

- **DIGNITY HEALTH** is buying **U.S. HealthWorks**, which will extend Dignity's reach to 172 occupational health medicine and urgent-care centers in 16 states.

- **EDWARDS LIFESCIENCES' Intuity –** The FDA granted a conditional investigational device exemption (IDE) for this new aortic heart valve with rapid-deployment technology. The 500-700-patient TRANSFORM trial is planned. Intuity already has a CE Mark.

- **GLAXOSMITHKLINE** and **THERAVANCE's umeclidinium bromide + vilanterol –** The companies announced positive results from four Phase III trials of this investigational combination of a LAMA (long-acting muscarinic antagonist) and a LABA (long-acting beta agonist) in treating patients with chronic obstructive pulmonary disease (COPD).

- **INVIVO THERAPEUTICS** asked for another meeting with the FDA to discuss its hydrogel platform for treating acute and sub-acute pain in the legs, neck, back, and arms. The company met with the FDA in April 2012 about its IDE for a biopolymer scaffolding for treating acute spinal cord injuries.

- **JOHNSON & JOHNSON/JANSSEN's bedaquiline –** A 600-patient, 9-month, placebo-controlled Phase III trial of this investigational drug to treat multidrug-resistant tuberculosis is planned. This would reduce the treatment time from the current 18-24 months to ~9 months.

- **LINDE**, a German industrial gas producer, is buying **Lincare Holdings**, a Florida-based provider of oxygen and respiratory therapy services to patients at home.

- **MDXHEALTH** is developing a companion test to identify brain tumor patients who will benefit most from **Merck KGaA's cilengitide**.

- **MICROTRANSPONDER's Serenity System** – The company reported that this wireless neurostimulation system successfully treated patients with tinnitus in a Phase I trial, and it plans to continue development.

- **NOVARTIS' Gilenya (fingolimod)** – An analysis of MRI data from the 1,272-patient FREEDOMS trial, published in the ***Archives of Neurology***, found that this sphingosine 1-phosphate receptor (S1PR) modulator not only decreased relapses and disability progression in multiple sclerosis (MS), but it also had a positive impact on long-term disease evolution.

- **NUPATHE's Zelrix (transdermal sumatriptan)** – The company said it has completed all chemistry, manufacturing, and controls (CMC) and development work needed to resubmit this investigational migraine drug to the FDA. In August 2011, the FDA rejected Zelrix, issuing a complete response letter, which the company said raised CMC questions.

- **ONYX PHARMACEUTICALS' Kyprolis (carfilzomib)** – The company has started enrolling patients in the 833-patient Phase III ENDEAVOR trial of carfilzomib + dexamethasone vs. **Roche's Velcade** (bortezomib) + dexamethasone in relapsed multiple myeloma. The FDA PDUFA date is July 27, 2012.

- **PFIZER's Zithromax (azithromycin)** – The FDA warned Pfizer that its brochure for this antibiotic was false or misleading because it omitted and minimized important risk information, made unsubstantiated superiority claims, omitted material facts, broadened the indication for the drug product, and made misleading and unsubstantiated claims. Pfizer said it stopped using the patient education brochure.

- **PROVECTUS PHARMACEUTICALS' PV-10** – The company said this novel formulation of Rose Bengal stain produced objective responses in 50% of metastatic melanoma patients in an 80-patient Phase II trial, and half of the responders had complete responses.

- **SALIX's Provir (crofelemer)** – **Napo Pharmaceuticals** wants to end its agreement with Salix and take back control of this anti-diarrhea drug for HIV patients. Napo is alleging that Salix delayed the development of crofelemer for HIV patients – and chose not to develop it for irritable bowel syndrome – to protect its own **Xifaxan** (rifaximin). Salix vowed to fight the lawsuit and said it plans to continue with development and commercialization of crofelemer.

- **TAKEDA's Actos (pioglitazone)** – A new meta-analysis of 10 trials – conducted by Canadian researchers and published in the ***Canadian Medical Association Journal (CMAJ)*** – found that this drug for Type 2 diabetes raises the risk of bladder cancer by 22%, but the increase was not statistically significant, and it was unclear whether the problem is a class effect for all thiazolidinediones (TZDs) or just applies to Actos.

- **THROMBOGENICS' ocriplasmin** – The FDA granted priority review to this intravitreal injection treatment for symptomatic vitreomacular adhesion including macular hole.

- **WALGREENS** is buying 144 retail pharmacies (including USA Drug, Super D, and May's) in the mid-South from **Stephen L. LaFrance Holdings**.

NEWS IN BRIEF

AETNA – sued by California doctors

A number of medical groups and physicians in California – including the Los Angeles County Medical Association and the California Medical Association – are suing Aetna, saying it routinely denies coverage for patients using out-of-network providers, even though the patients' policies clearly say they can see out-of-network providers. The lawsuit also alleges that Aetna threatens doctors with contract termination if they refer patients outside the network.

Aetna said the doctors are suing the insurer to retaliate for Aetna suing some of them earlier this year for "egregious billing practices" – e.g., enticing patients to have procedures performed at out-of-network facilities without telling the patients they had an ownership stake in that facility and leading to wildly inflated bills.

ALLERGAN's Botox (onabotulinumtoxinA) – efficacy in MS tremors

A 23-patient crossover study published in ***Neurology*** found that Botox significantly and dose-dependently reduced upper-limb (arm and hand) tremor in multiple sclerosis (MS) patients by 6 weeks vs. placebo, and the improvements were maintained at 12 weeks. Patients saw improvement in their ability to write and draw, for example. Botox was associated with significantly more limb weakness vs. placebo (42.2% vs. 6.1%), but the weakness was mild or moderate in all cases and generally resolved within 2 weeks. A Phase III trial is planned.

DHS – develops foot-and-mouth vaccine for U.S.

According to a report in ***Science Now***, the Department of Homeland Security (DHS) announced that it has developed the first vaccine for foot-and-mouth disease that can be manufactured and licensed in the United States and that could be used in the event of an outbreak of the disease in this country. The vaccine, which was developed at DHS' Plum Island Animal Disease Center, consists of proteins that produce an immune response to the virus, but there is no genetic material, so the capsid is not infectious and does not cause disease.

KV Pharmaceutical's Makena (hydroxyprosterone caproate) – sued the FDA

The company filed a lawsuit against the FDA for failing to limit compounded versions of this drug to prevent premature birth. KV claimed the FDA was addressing the needs of insurers instead of patients and taking cost into account, which KV said the law doesn't allow, by not preventing pharmacies from compounding less-expensive versions of Makena. In June, the FDA said it found no safety issue with compounded versions of Makena, despite the company's concerns about potency and purity. KV said it will go bankrupt if the FDA doesn't limit compounding in the next 3-6 months because Makena sales are not sufficient to keep the company afloat.

REGULATORY NEWS

FDA proposing UDIs for medical devices

The FDA wants most medical devices distributed in the U.S. to have a unique device identifier (UDI) that includes a numeric or alphanumeric code for the device model, a production identifier with information such as lot or batch number, and serial number or expiration date. The FDA hopes a UDI system will help the Agency identify product problems more quickly, better target recalls, and improve patient safety. The FDA ran four pilot studies before issuing its proposed rule, which is now open for comment for 120 days.

Affected devices include stents, catheters, defibrillators, and artificial joints. Exempted devices include bedpans and over-the-counter products. Device manufacturers would be required to have UDIs on the label or packaging of their affected products within one year of the final rule and on the device itself within three years.

The UDI information would be stored in a publicly available UDI database, but no identifying patient information would be stored in that device information center. The FDA is proposing to phase in implementation, focusing on the highest-risk medical devices first and exempting low-risk devices from some or all of the requirements. Over-the-counter (OTC) devices sold at retail would be exempt.

Jeffrey Shuren, MD, director of the FDA's Center for Devices and Radiological Health (CDRH), said, "We've never been able to make that link between the device and the patients' or practitioners' experience with that device until we have the UDI…The UDI is really the linchpin for modern postmarket surveillance for medical devices."

CMS changes rates for HOPDs and ASCs

CMS issued a proposed rule to update payment policies and rates for >4,000 hospital outpatient departments (HOPDs) and >5,000 ambulatory surgical centers (ASCs) starting in January 2013. Among the changes are:

- A 2.1% increase in HOPD payment rates.
- A 1.3% increase in ASC rates.
- Streamlining of the Quality Improvement Organizations (QIOs) to make them more responsive to beneficiary complaints about quality of care by giving beneficiaries more information about the QIO review process and creating a new alternative dispute resolution option, called Immediate Advocacy, to resolve complaints.

The proposed rule will appear in the ***Federal Register*** on July 30, 2012, and CMS will accept comments until September 4, 2012, with a final rule to be issued by November 1, 2012.

FDA to make adverse event reporting easier

The FDA is working on an application that would let consumers and clinicians use smartphones to instantly report adverse events related to medical devices. The free app is slated to be publicly available later this year.

FDA targets unapproved oxycodone products

In the latest action in its Unapproved Drugs Initiative, the FDA issued a Federal Register notice instructing companies to stop manufacturing and/or distributing unapproved, single-ingredient, immediate-release drugs that contain the opioid oxycodone (tablets, capsules, and oral solutions). The FDA called it a "high public health priority" to get these unapproved products off the market. The Agency does not expect any problems for patients with this action because there are FDA-approved oral dosage forms that patients can be prescribed instead.

Manufacturing must stop within 45 days and distribution within 90 days. Companies that continue to market these products after this will be subject to seizure, injunction, or other action. In 2009, the FDA sent warning letters to companies manufacturing these unapproved products, and the Agency does not plan to issue any additional warning letters before taking action.

The FDA also warned companies not to reformulate their products into unapproved new drugs without oxycodone and market them under the same name or substantially the same name (including a new name that contains the old name), saying that could confuse patients and doctors.

Legislation to spur development of drugs for childhood cancer

A bill, sponsored by Rep. Michael McCaul (R-TX) and likely to be signed by President Barack Obama, will offer drug companies incentives to pioneer medications for rare childhood diseases that afflict too few kids to be profitable. In return for developing drugs for these small patient populations, pharmas will be able to earn vouchers for faster FDA approval of new and potentially more profitable drugs.

CMS changing ESRD policy/payment

The Centers for Medicare and Medicaid Services (CMS) proposed updated rules and payment changes for end-stage renal disease (ESRD) facilities (dialysis centers) that would begin in January 2013. The changes include:

- A 2.5% increase in outpatient maintenance dialysis treatment rates. When all policy changes are considered together, CMS estimates that payments to dialysis facilities will increase by 3.1% in 2013.
- As part of the Quality Incentive Program (QIP), dialysis centers would be required to collect data for four reporting measures:
  - Anemia.
  - Dialysis infections, which need to be reported to the Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN).
  - Phosphorous and calcium levels.
  - Patient surveys of care.
- The composite drug add-on adjustment is reduced from 14.3% to 14.0% to maintain the drug add-on at $20.33.

CMS noted that 90% of dialysis centers are voluntarily receiving payments under the new bundled system. Comments on the proposed changes can be made until August 31, 2012.

FDA approvals/clearances

- **ACTELION PHARMACEUTICALS' Veletri (epoprostenol)** – A second-generation injectable version was approved to treat pulmonary arterial hypertension (PAH).
- **ORASURE TECHNOLOGIES' OraQuick In-Home HIV Test**, the first over-the-counter, self-administered HIV test kit, was approved.
- **PROPEP SURGICAL's ProPep Nerve Monitoring System**, a nerve-monitoring device for use in robot-aided surgeries (e.g., **Intuitive's da Vinci**), received 510(k) clearance. It already has a CE Mark.
- **QIAGEN's therascreen KRAS RGQ PCR Kit**, a genetic test for the KRAS mutation, was approved for use in patients with metastatic colorectal cancer (mCRC) considering therapy with Bristol-Myers Squibb and Lilly's Erbitux (cetuximab) since studies have found that Erbitux is not effective in those who have the mutation. The FDA simultaneously approved a new indication for Erbitux for use in combination with FOLFIRI as a first-line treatment for patients with mCRC with EGFR-expressing, KRAS wild-type tumors.
- **R4 VASCULAR's Vector Percutaneous Transluminal Angioplasty balloon catheter**, which is designed to be seen on an x-ray without the use of contrast media, was cleared for use.
- **ROCHE's TaqMan CMV Test** – This is the first DNA test approved to help healthcare professionals gauge the progress of antiviral treatment in solid organ transplant patients undergoing cytomegalovirus (CMV) antiviral therapy.

FDA recalls/warnings

- **BEDFORD LABORATORIES' leucovorin calcium injection** – The company voluntarily recalled this hospital-use drug due to the discovery of visible crystalline particulate matter in a small number of vials in some lots.
- **CAREFUSION's AirLife Infant Breathing Circuit** – The FDA classified this voluntary action – due to a danger of cracks that can cause a leak – as a Class I recall. The new design avoids this issue.
- **MAQUET CRITICAL CARE and MAQUET MEDICAL SYSTEMS USA's Flow-i Anesthesia System** – A Class I recall was issued about a software problem with the switch used for changing between manual and automatic ventilation modes.

European regulatory news

- **BRAINSWAY's Deep TMS**, which transmits targeted magnetic pulses deep into the brain, was granted a CE Mark to treat patients with neuropathic chronic pain. It already has a CE Mark for use in Parkinson's disease, clinical depression, post-traumatic stress disorder, bipolar disorder, and schizophrenia.
- **EMA investigation** – The European Medicines Agency (EMA) is investigating whether there is a potential conflict of interest with its former chief counsel Vincenzo Salvatore, who left the agency in June and has since been named senior counsel to U.S.-based Sidley Austin's European life sciences regulatory practice. Salvatore said the appointment had been approved by the EMA, but EMA executive director Guido Rasi reportedly denied that.
- **FOREST LABORATORIES' Celexa (citalopram)** – An EMA study found that this antidepressant is three times more likely to cause cardiac abnormalities, particularly QT prolongation, than other antidepressants. The study also found the risk of Torsade de Pointes was increased three-fold with Celexa vs. other SSRIs. As a result, the EMA advised that the maximum dose was being lowered to 40 mg from 60 mg (with 20 mg the top dose for elderly patients).

U.K.'s National Institute for Health and Clinical Excellence (NICE) news

ROCHE's Avastin (bevacizumab) – NICE rejected use of Avastin in combination with **Xeloda** (capecitabine) as a first-line treatment for advanced breast cancer, saying there are no data showing an improvement in overall survival and/or patient quality of life, so it is not cost-effective.

Regulatory news from other countries

Japan: The American Medical Device and Diagnostics Manufacturers' Association in Japan is considering creation of a regulatory structure for medical devices that is separate from drugs. The proposal, which is part of an effort to update Japan's Pharmaceutical Affairs Law, is expected to be introduced at the next session of the Diet in January 2013.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	July 2012	
July 9	**Pozen's PA-32540** (immediate-release omeprazole + extended-release aspirin)	Company call with the FDA to discuss the regulatory pathway
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' Kyprolis** (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
	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** (tilmanocept), a radioactive agent for tracing lymph nodes in cancer patients	PDUFA date (extended from June 10)
September 14	**Gilead Sciences' Truvada PrEP** HIV therapy to help prevent the transmission of HIV to healthy people	PDUFA date (extended from June 15)
September 23	**Regeneron's Eylea** (aflibercept) for central retinal vein occlusion (CRVO)	PDUFA date
October 12	**Celgene's Abraxane** (nab-paclitaxel) to treat NSCLC	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)	PDUFA date (extended from July 29)
October 29-31	**Bayer's regorafenib** for metastatic CRC	PDUFA date
December 21	**Alexa Pharmaceuticals' Adasuve** (loxapine) for agitation associated with schizophrenia or bipolar disorder	PDUFA date
December 28	**Biogen Idec's BG-12** for multiple sclerosis	PDUFA date
	2013	
January 29	**Sanofi/Genzyme and Isis Pharmaceuticals' Kynamro** (mipromersen) for homozygous familial hypercholesterolemia	PDUFA date
January 30	**Raptor Pharmaceutical's cysteamine bitartrate** delayed-release (RP-103) to treat nephropathic cystinosis	PDUFA date
February 10	**Celgene's pomalidomide** for relapsed/refractory multiple myeloma	PDUFA date
February 24	**Dynavax's Heplisav** hepatitis B vaccine	PDUFA date
April 11	**Sanofi/Genzyme and Bayer's Lemtrada** (alemtuzumab) for multiple sclerosis	PDUFA date