TRENDS-in-MEDICINE

February 17, 2013

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

- **ABLYNX's ALX-0061** – The company announced positive 24-week results from a 37-patient Phase II trial of this anti-IL-6R nanobody in rheumatoid arthritis, with 100% of patients on 3 mg/kg Q4W achieving ACR20, 75% ACR50, and 63% ACR70. In addition, 75% of patients achieved DAS28.

- **ADVANCED CELL TECHNOLOGY** – The company's clinical partner, the University of California, Los Angeles, obtained FDA approval for a 12-patient trial to evaluate the safety of subretinal implantation of human embryonic stem cell-derived cells to treat severe myopia.

- **Allopurinol**, a generic xanthine oxidase inhibitor, reduced cardiovascular morbidity and all-cause mortality in patients with hypertensive nephropathy in a 187-patient study published in the journal ***Clinical and Experimental Nephrology***, with cardiovascular events/deaths 10.4% with allopurinol vs. 18.9% without it.

- **ASTRAZENECA's selumetinib (AZD-6244)** – A small proof-of-concept study published in the ***New England Journal of Medicine*** found that this kinase inhibitor sensitized advanced thyroid cancer to radioiodine, particularly in patients with RAS mutations. Selumetinib increased or restored the uptake of iodine based on PET imaging in 60% of patients previously refractory to radioiodine.

- **BAYER's riociguat (BAY-63-2521)** – The company submitted a new drug application to both the FDA and the European Medicines Agency (EMA) for approval of this investigational drug to treat both chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH).

- **BIOGEN IDEC's Tysabri (natalizumab)** – According to a report in ***Neurology***, a Swedish multiple sclerosis patient died from a reaction to anti-natalizumab antibodies. The researchers reported that she developed "significant neurological abnormalities" after six Tysabri infusions, concluding that her death was from "rebound neuroinflammation" from anti-natalizumab antibodies.

- **BRISTOL-MYERS SQUIBB** sold exclusive marketing rights in Mexico and Latin America to six over-the-counter drugs to **Reckitt Benckiser**, which has the option to buy the drugs outright in three years. BMS will continue to make the drugs, which include **Picot** (antacid), **Tempra** (pain reliever), and **Graneodin** (cold and cough).

- **CANGENE's BAT (botulinum antitoxin)** – The FDA's Blood Products Advisory Committee voted unanimously (14-0) to recommend approval of this anti-bioterrorism agent, which Cangene currently provides to the government under an emergency use exemption. However, the panel expressed strong concerns about its use in children.

- **CARDINAL HEALTH** is buying **AssuraMed**, a mail order and home-delivery medical supply company.

- **Chemotherapy** – A study by the National Cancer Institute (NCI), published in ***Blood***, linked chemotherapy to an increased risk of acute myeloid leukemia (AML). The researchers examined data for ~426,000 patients who had cancer chemotherapy from 1975-2008. They found that non-Hodgkin's lymphoma survivors were at greater risk for AML, but since 2000, patients treated for esophageal, prostate, and cervical cancer also were at greater risk of AML. The study also found that since the 1990s, patients treated for cancer of bones and joints as well as the endometrium were at increased risk for AML.

- **CIPLA** is delaying its acquisition of South Africa-based drugmaker **Cipla Medpro** due to valuation issues.

- **Computerized diagnosis** – IBM's supercomputer, Watson, is now being used by Memorial Sloan-Kettering Cancer Center to recommend the best drug treatment option for patients with Stage IV adenocarcinomas. *Stay tuned for results in computer vs. oncologist.*

- **EISAI's lenvatinib (E-7080)** – This investigational drug to treat thyroid cancer was granted orphan drug status.

- **Generic drug labels** – According to a story in Pharmalot.com's ***Pharma Blog***, a Justice Department friend-of-the-court brief in a generic drug case had this footnote: "This office has been informed that FDA is considering a regulatory change that would allow generic manufacturers, like brand-name manufacturers, to change their labeling in appropriate circumstances."

- **ICD leads** – A retrospective study, published in ***HeartRhythm***, by researchers in Italy found that implantable cardioverter defibrillators with thin leads – i.e., **St. Jude Medical's Riata** and **Medtronic's Sprint Fidelis** – are at greater risk of failure than standard-diameter leads:
  - Fidelis 4.8% vs. 0.8%, p<0.001.
  - Riata 2.6% vs. 0.8%, p=0.001.

The researchers said the problem with the Riata and Fidelis leads may be related more to their size than to their mechanics.

- **JENNEREX's Pexa-Vec (JX-594)** – This genetically modified smallpox vaccine shrank tumors in advanced hepatocellular carcinoma patients and extended survival more than a year in a study published in ***Nature Medicine***. In the study, 16 patients on high dose survived an average of 14.1 months vs. 6.7 months for the 14 patients on low dose. Both doses were well tolerated.

- **MEDTRONIC's Kinetra and Soletra** – A study published in the ***New England Journal of Medicine*** found that patients with early Parkinson's disease who still respond to drug therapy saw an improvement in symptoms and quality of life with deep-brain stimulation (DBS). The researchers reported that quality of life improved with drugs + DBS but declined slightly with drugs alone.

- **NOVARTIS' Gilenya (fingolimod)** – The FDA approved an application by the non-profit ALS Therapy Development Institute to start a ~250-patient Phase IIa trial of this multiple sclerosis treatment in amyotrophic lateral sclerosis (ALS). For this study, the drug is being called TDI-132.

- **NOVO NORDISK's Tresiba (insulin degludec) and Ryzodeg (insulin degludec + insulin aspart)** – The FDA rejected these two oral Type 2 diabetes drugs, issuing a complete response letter requiring a cardiovascular safety trial before approval. Novo Nordisk also must resolve a warning letter on one of its plants before the drugs can be approved.

- **NSAIDs** – A study published in ***PLOS Medicine*** found that diclofenac is just as likely to cause a heart attack as **Merck's Vioxx** (rofecoxib), which was taken off the U.S. market, but use of diclofenac has not declined. In fact, ~5 million prescriptions are written for diclofenac annually.

- **ONCOLYTICS BIOTECH's Reolysin (wild-type reovirus; serotype 3 Dearing)** – The company announced that a 21-patient Phase II trial of this intravenous drug in combination with carboplatin and paclitaxel had positive results in squamous cell carcinoma of the lung (SCCLC), with partial response in 9 patients and stable disease in 9, for a disease control rate of 86%. In addition, 95% of patients had "significant tumor shrinkage." Previously, the drug was shown to be active in head and neck and colorectal cancers.

- **PEREGRINE PHARMACEUTICALS' bavituximab** – The company announced that a Phase II trial in pancreatic cancer showed a "modest" improvement in overall survival with the addition of bavituximab to **Lilly's Gemzar** (gemcitabine) – 5.6 months vs. 5.2 months for Gemzar alone.

- **PFIZER** is closing its research facility in Singapore, laying off ~30 people.

- **PHARMACYCLICS and JOHNSON & JOHNSON/JANSSEN's ibrutinib**, an investigational drug to treat relapsed/refractory mantle cell lymphoma and Waldenstrom's macroglobulinemia, was granted "breakthrough" status by the FDA. The companies plan to submit the drug to the FDA by the end of 2013.

- **QIAGEN** and **LILLY** are collaborating on the development and commercialization of companion diagnostics for Lilly drugs (investigational and approved) across all therapeutic areas.

- **RECOR MEDICAL's Gen-2 Paradise** – The company started a 50-patient, postmarket study in Europe of this second-generation, 6 Fr, over-the-wire ultrasound renal denervation device.

- **SANOFI** is buying a bigger share of **Regeneron** (upping its 16.7% share, with a maximum possible of 30%).

- **THER-RX's Makena (hydroxyprogesterone caproate injection)** – A 161-patient study presented at the Society for Maternal-Fetal Medicine found that 17-P injections do not prevent preterm birth in women who are pregnant with twins – and could even be harmful, increasing the rate of preterm delivery before 34 weeks.

- **TRIUS THERAPEUTICS' tedizolid** – A study published in the ***Journal of the American Medical Association*** found that this investigational antibiotic is as effective as linezolid against bacterial skin infections, and the duration of treatment is shorter with tedizolid: 200 mg tedizolid QD for 6 days was statistically non-inferior to 600 mg linezolid BID for 10 days.

NEWS IN BRIEF

Alzheimer's disease – beta-amyloid theory wobbles

In what could be a serious blow to the whole beta-amyloid theory of Alzheimer's disease causation, researchers at the University of California, Davis, found that vascular brain injury, not beta-amyloid, affects brain function, cognition, and development of mild cognitive impairment (MCI). The researchers found no association between beta-amyloid on PET scans and cognitive impairment. There was also no evidence that brain infarcts led to beta-amyloid deposition, or vice versa.

MERCK

- **Vorapaxar.** A subanalysis of the TRA 2°P-TIMI-50 trial, published in the journal ***Stroke*** and presented at the International Stroke Conference, found that adding this anti-platelet agent to standard therapy for secondary stroke prevention may not benefit patients with a recent history of ischemic stroke. In the analysis, prior stroke patients given vorapaxar had a higher rate of cardiovascular death, myocardial infarction, or stroke during follow-up vs. those who received standard therapy alone (13% vs. 11.7%). In addition, bleeding rates were higher with the addition of vorapaxar (4.2% vs. 2.4%), as was intracranial hemorrhage (2.5% vs. 1%).

- **Zostavax.** A 92-patient study published in the journal ***Clinical Infectious Diseases*** found that this shingles vaccine is less effective in people with untreated depression. After getting the vaccine, cell-mediated immunity increased 70% in normal controls, 288% in treated major depressive disorder (MDD) patients, and didn't change in untreated MDD patients. Treating the depression appears to normalize the immune response to the vaccine, increasing its efficacy.

What sequestration would mean for healthcare

If Congress doesn't get its act together and prevent sequestration from happening, some of the impacts on healthcare will include:

- The National Institutes of Health budget would be cut by 5.1%, causing it to delay or halt scientific projects and make hundreds of fewer research grants.

- ~12,000 research positions that are funded by NIH grants would be cut.

- ~373,000 people with mental illness would no longer be able to get treated because of reductions in the Mental Health Block Grant.

- FDA approvals of new drugs could be delayed.

- The FDA would conduct 2,100 fewer inspections of food manufacturing firms this year.

- Health departments will give 424,000 fewer tests for the AIDS virus this year.

- About 7,400 fewer HIV patients will receive lifesaving medication through the AIDS Drug Assistance Program.

REGULATORY NEWS

FDA "breakthrough" status update

In an interview with ***Bloomberg***, Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research (CDER), said that drugs granted "breakthrough" status might be able to gain approval with a single round of studies, rather than Phase I, II, and III trials. So far, three

drugs have been granted "breakthrough" status, and 18 others have applied for that status.

FDA commissioner gets new deputy

Richard Moscicki, MD, is the new deputy director for science operations at the FDA's Center for Drug Evaluation and Research (CDER). He was formerly senior vice president for clinical development and medical affairs at Genzyme. Dr. Moscicki did a fellowship in immunology and immunopathology at Massachusetts General Hospital (MGH), and he will remain on the staff at MGH and on the faculty of Harvard Medical School. This appointment gives FDA Commissioner Margaret Hamburg, MD, a trio of deputies: Dr. Moscicki; Douglas Throckmorton, MD, deputy director for regulatory programs; and Robert Temple, MD, deputy director for clinical science.

FDA drug safety watch list grows

Three drugs were added:

- **GlaxoSmithKline's Arzerra (ofatumumab)**, a leukemia drug – concern is viral infections.
- **UCB's Vimpat (lacosamide)**, an epilepsy drug – issue is neutropenia.
- **Acorda Therapeutics' Ampyra (dalfampridine)**, a multiple sclerosis drug – issue is anaphylaxis.

FDA oversight of REMS criticized

The Office of the Inspector General (OIG) of the Department of Health and Human Services (HHS) issued a report that questions the effectiveness of the risk evaluation and mitigation strategies (REMS) the FDA requires for some drugs as part of their approval. The FDA approved 199 REMS from the time the program became mandatory in 2008 through 2011. The OIG reviewed 49 of the 99 REMS that were still in place in 2012 and found:

- Nearly half did not include all the required information.
- Ten were not submitted to the FDA within the required timeframe.
- Only seven met all of the goals.
- Most REMS did not meet their goals because of deficiencies in patient and prescriber awareness of drug risks.
- Nearly all deficiencies identified in a prior assessment were still present in the sponsor's most recent assessment.
- The FDA has not identified reliable methods to evaluate the effectiveness of a REMS.
- The FDA is supposed to evaluate the Elements to Assure Safe Use (ETASU) of at least one REMS each year but has only done one ETASU evaluation since 2008.
- The FDA does not have the authority to take enforcement action against sponsors that do not include all the requested information.

The OIG wants Congress to give the FDA more authority, so the agency can make its assessment plans enforceable.

IOM calls for national drug-tracking system

The Institute of Medicine (IOM) released a report, commissioned by the FDA, that found that fighting fake drugs will require creation of a national drug-tracking system. The IOM report called for putting medication through "a chain of custody like U.S. courts require for evidence in a trial." The IOM also said oversight of prescription drug wholesalers needs to be strengthened. FDA Commissioner Dr. Hamburg said the FDA is already implementing many of the IOM's suggestions.

Members of Congress are considering legislation to increase the crackdown on fake drugs and improve oversight, perhaps modeled after California state legislation, which requires individual units of drugs to be accounted for at each step in the supply chain.

FDA approvals/clearances

- **BAUSCH + LOMB's Victus femtosecond laser** received expanded 510(k) clearance for use in making accurate surgical cuts in the cornea.
- **INTUITIVE IMAGING INFORMATICS' ImageQube PACS** application was cleared for use.
- **LIFE TECHNOLOGIES' SeCore HLA typing kits and 3500 Dx Genetic Analyzers** – Both of these sequencing-based tools received 510(k) clearance.
- **MEDTRONIC's Advisa DR MRI SureScan**, a next-generation MRI-safe pacemaker, was approved.
- **OPTOVUE's iVue SD-OCT** – Incorporation of a normative database into this imaging device was cleared for use.
- **PARAGONIX TECHNOLOGIES' Sherpa Pak Cardiac Transport System**, a new device for transporting donor hearts, was cleared for use.
- **PLANMED's Verity Extremity Scanner**, which uses 3D imaging to find subtle fractures in the extremities, was cleared for use.

- **SECOND SIGHT MEDICAL PRODUCTS' Argus II Retinal Prosthesis System** – The FDA granted a humanitarian device exemption for this implanted device to treat adult patients with advanced (severe-to-profound) retinitis pigmentosa. The device does not restore vision, but it may allow patients to detect light and dark, so they can identify the location or movement of objects or people. Development of the Argus II was supported by grants from the Department of Energy, the National Eye Institute at the National Institutes of Health, and the National Science Foundation. William Maisel, MD, deputy director for science and chief scientist at the FDA's Center for Devices and Radiological Health (CDRH), wrote about the device in a blog on the FDA website, offering very high praise for this device, which could help up to 1,300 people a year.

FDA recalls/warnings

- **GE HEALTHCARE's Giraffe and Panda T-Piece Resuscitation Systems and Mask Resuscitation Systems** – The recall of these devices was upped to a Class I recall because the oxygen and air wall inlet fittings and/or labels may have been reversed during assembly.
- **HOSPIRA** – The company received a Form 483 notice about quality and manufacturing issues at its headquarters in Lake Forest IL.
- **JOHNSON & JOHNSON/DEPUY ORTHOPAEDICS' Adept** – The company recalled this all-metal hip implant after a review of national registries in the U.K. and Australia found a higher-than-expected number had to be replaced (12.1% in the U.K within 7 years, 7.1% in Australia within 3 years).
- **ST. JUDE MEDICAL's Amplatzer TorqVue FX Delivery System** – A Class I recall was issued because this septal closure delivery system may fracture, causing serious damage and even death. The company said no deaths have been reported but urged doctors to stop using it.

European regulatory news

- **CURVEBEAM's pedCAT CT scanner**, which is used for 3D imaging of feet and ankles, was granted marketing approval.
- **GLAXOSMITHKLINE's trametinib (GSK-1120212)** – The company filed an application with the EMA for approval to use this MEK inhibitor as monotherapy as well as in combination with dabrafenib (GSK-2118436), a BRAF inhibitor, in metastatic melanoma patients with a BRAF V600 mutation, and the EMA's Committee for Medicinal Products for Human Use (CHMP) granted accelerated review.
- **TRUE DIAGNOSTICS' TrueDXPSA**, a point-of-care quantitative test for prostate-specific antigen (PSA), received a CE Mark.
- The European Parliament Environment, Public Health, and Food Safety (ENVI) Committee is considering a revision of the European Clinical Trials Directive (EUCTD). Among the proposed changes are:
  - Allow co-sponsors of trials. Currently, one institution has to take legal responsibility for each trial. This would let investigators share the work for a trial.
  - Allow co-sponsors outside of Europe who can deal with local legal issues relating to a trial. This could encourage global recruitment.
  - Create a single European portal for submitting applications and creating European databases.
  - Allow one member state to be the main contact point for the sponsor, coordinating the response of all the member states involved. However, the plan would still continue the practice of independent assessments by individual member states.
  - Set strict timelines for submissions, assessments, and decisions on clinical trials.
  - Recognize that informed consent is not needed in a trial in emergency situations (e.g., when patients have a myocardial infarction).

The European Society of Cardiology also proposed that the new rules require that:

- Clinical trial populations reflect the diversity of real-life populations – with the elderly, both genders, and ethnic minorities represented.
- Cardiovascular imaging be encouraged in trials.

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

NOVARTIS' Jakavi (ruxolitinib) – In a preliminary recommendation, NICE rejected this myelofibrosis drug, saying the economic model the company used overstated the drug's benefit vs. its cost ($67,000/year). Novartis has 30 days to submit a response before NICE submits an updated recommendation to the National Health Service (NHS).

Regulatory news from other countries

- ***China:*** **CELGENE's Revlimid (lenalidomide)** was approved for use in combination with dexamethasone to treat patients with relapsed/refractory multiple melanoma after ≥1 prior treatment.

- ***Japan:*** Japan loosened the stability testing requirements for medical devices, in most cases no longer requiring stability testing data before approval. Some devices will still require the data, including those that contain certain raw materials, biological products, and radioactive material.
- ***Mexico:*** **HALT MEDICAL's Acessa System**, a radio-frequency system for treating uterine fibroids, was approved.
- ***Sweden:*** The Swedish Medical Products Agency released new guidance outlining its process for regulating standalone software classified as medical devices.

2013 FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
February 22	**NeuroPace's RNS system,** a neuromodulation system for epilepsy	FDA's Neurological Devices Advisory Committee
February 24	**Dynavax's Heplisav** hepatitis B vaccine	PDUFA date
February 26	**Roche/Genentech** and **ImmunoGen's trastuzumab emtansine** (T-DM1) to treat unresectable locally advanced or metastatic HER2+ breast cancer	PDUFA date
February 28	**Lundbeck** and **Otsuka's aripiprazole depot** to treat schizophrenia	PDUFA date
March 1	**Zogenix's Zohydro** (extended-release hydrocodone) for chronic pain	PDUFA date
March 4	**Depomed's gabapentin** and **Noven Therapeutics' paroxetine** – both to treat moderate-to-severe vasomotor symptoms of menopause	FDA's Reproductive Health Drugs Advisory Committee
March 5	Efficacy vs. cancer risk with calcitonin-salmon products **– Novartis' Miacalcin** (calcitonin-salmon – injection and nasal spray) and **Upsher-Smith Laboratories' Fortical** (calcitonin-salmon recombinant nasal spray) – for the treatment of postmenopausal osteoporosis	Joint meeting of the FDA's Reproductive Health Drugs Advisory Committee and the FDA's Drug Safety and Risk Management Advisory Committee
March 7	**GlaxoSmithKline's Breo Ellipta** (fluticasone furoate + vilanterol), a dry powder inhaler for chronic obstructive pulmonary disease (COPD)	FDA's Pulmonary-Allergy Drugs Advisory Committee
March 17	**Bristol-Myers Squibb** and **Pfizer's Eliquis** (apixaban,) an oral anticoagulant to prevent stroke in atrial fibrillation patients	PDUFA date
March 18	**Pharmaxis' Bronchitol** (mannitol) for cystic fibrosis	PDUFA date
March 20	**Abbott's MitraClip** for mitral valve repair	FDA's Circulatory System Devices Advisory Committee
March 22	**Cangene's BAT** (botulinum antitoxin), an anti-bioterrorism agent	PDUFA date
March 28	**Biogen Idec's BG-12** (dimethyl fumarate) for multiple sclerosis	PDUFA date (extended from December 28, 2012)
March 31	**Johnson & Johnson's Invokana** (canagliflozin), a SGLT2 inhibitor to treat Type 2 diabetes	PDUFA date
April 15	**MAP Pharmaceuticals' Levadex** (dihydroergotamine), inhaled migraine drug	PDUFA date
April 29	**Shire's Vyvanse** (lisdexamfetamine dimesylate), sNDA for ADHD treatment in children	PDUFA date
April 29-30	Discussion of **medical device labeling standardization**, including an online labeling repository for in-home medical devices	FDA public workshop
April 30	**Raptor Pharmaceutical's cysteamine bitartrate** delayed-release (RP-103) to treat nephropathic cystinosis	PDUFA date (extended from January 30, 2013)
May 12	**GlaxoSmithKline** and **Theravance's Breo/Relvar** (fluticasone furoate + vilanterol) to treat chronic obstructive pulmonary disease (COPD)	PDUFA date
May 31	**DepoMed's Serada** (gabapentin extended-release), a hot-flash treatment	PDUFA date
June 20	**Dainippon Sumitomo Pharma/Sunovion Pharmaceuticals' Latuda** (lurasidone), a schizophrenia drug for use in treating bipolar disorder	PDUFA date
July	**PET imaging** of brain beta-amyloid	CMS coverage decision expected
July 28	**Aveo Oncology** and **Astellas Pharma's Tivopath** (tivozanib) to treat advanced renal cell carcinoma	PDUFA date
October 2	**Lundbeck** and **Takeda's Brintellix** (vortioxetine), an antidepressant for major depressive disorder	PDUFA date
October 19	**Actelion's Opsumit** (macitentan), a dual endothelin receptor antagonist to treat pulmonary arterial hypertension	PDUFA date