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

- **ACCELERON PHARMA and CELGENE's ACE-536** was granted orphan drug status by the FDA to treat two rare blood disorders, beta-thalassemia and myelodysplastic syndromes.

- **A.P. PHARMA's granisetron (APF-530)** – The FDA rejected this treatment for chemotherapy-induced nausea and vomiting, issuing a complete response letter that asked for (a) an additional analysis of the Phase III trial data with patients reclassified as receiving moderately or highly vomit-inducing chemotherapy and (b) a study testing the usability of the syringe delivery system. In addition, the FDA cited manufacturing inspection deficiencies.

- **CYTORI** – The U.S. Court of Appeals in Washington sided with the FDA against Cytori, ruling that the FDA was correct to reject fast track approval for Cytori devices used to process adult stem cells. The judge wrote, "FDA concluded and explained that fat is not blood and that the difference matters. A court is ill-equipped to second-guess that kind of Agency scientific judgment. After careful review, we find FDA's assessment both reasonable and reasonably explained." The FDA had rejected the devices, saying they needed more testing.

- **GILEAD SCIENCES' sofosbuvir + ledipasvir** – The company released an update of the 24-week Phase III ION-1 trial of an all-oral combination of sofosbuvir (a once-daily NS5B nucleotide inhibitor) plus ledipasvir (a once-daily NS5A inhibitor) with or without BID ribavirin in patients with hepatitis C genotype 1 (HCV-1), saying the data safety monitoring board (DSMB) reviewed the safety and concluded that the trial could continue without modificiation. This means the SVR4 exceeded the predefined rate of 60%. Enrollment of the remaining 600 patients is underway.

- **GLAXOSMITHKLINE's H5N1 pandemic bird flu vaccine** – The FDA delayed making a decision on this vaccine, saying it needed more time to evaluate it. The company denied the delay was due to questions about links to narcolepsy with its H1N1 **Pandemrix** vaccine. And those questions escalated this week when Swedish researchers announced that the narcolepsy occurred in young adults (<age 30), not just children and teenagers, as previously thought. Sweden's Medical Products Agency said that the risk of narcolepsy was three times higher among those <age 20 and twice as high in those age 21-30 who got the vaccine vs. people who were not inoculated.

- **INTUITIVE SURGICAL's da Vinci** – More bad news for this surgical robot. A Washington state court judge refused to throw out a lawsuit brought over the death of a patient operated on using the robot, saying the state's product liability laws require medical device makers to properly train physicians who buy their products.

- **JOHNSON & JOHNSON/JANSSEN and MEDIVIR's simeprevir (TMC-435)** – This once-daily NS3/4A protease inhibitor was submitted to the FDA to treat genotype 1 hepatitis C virus (HCV-1) patients in combination with pegylated interferon and ribavirin (PR).

- **LIFE TECHNOLOGIES** licensed the rights to use its Lentiviral vector technology to **Medicyte GmbH** to develop its next-generation, cell-based Upcyte cell products.

- **LUNDBECK's Lu-AE-58054** – Lundbeck and **Otsuka** have agreed to collaborate on this investigational Alzheimer's drug and will start a >2,500-patient Phase III trial later this year to see if adding it to Pfizer's Aricept (donepezil) in mild-to-moderate patients will improve cognition. The results of a Phase II trial will be presented at the Alzheimer's Association International Conference (AAIC, formerly ICAD) in Boston in July 2013.

- **MERCK's allergy immunotherapy tablet (AIT)** – The FDA accepted Merck's biologics license application (BLA) for this investigational immunotherapy for grass pollen allergy, a sublingual dissolving tablet.

- **NOVARTIS' Zometa (zoledronic acid)** – In a study presented at the European Association of Urology Congress in Milan, Italy, Zometa missed the primary endpoint. Zometa was no better than standard treatment (control) in preventing bone metastases (13.7% vs. 13.0% p=0.721) or prolonging survival (p=0.717) in prostate cancer patients.

- **PHYTOPHARM's Cogane (PYM-50028)** – The company announced last month that this Parkinson's drug failed. After a review of the trial data, Phytopharm is giving up on it entirely and putting itself up for sale.

- **pSIVIDA and ALIMERA SCIENCES' Illuvien (fluocinolone intravitreal implant)** – The company said it plans to refile a new drug application (NDA) soon to treat diabetic macular edema. Illuvien was rejected by the FDA in 2011, but the company hopes new data it will submit with the NDA will change the FDA's mind.

- **REPROS THERAPEUTICS' Androxal (enclomiphene)** met the primary endpoint in a 151-patient Phase III trial, restoring normal testosterone levels to 79% of men with hypogonadism vs. placebo.

- **SANTARIS PHARMA's miravirsen** – Research published in the ***New England Journal of Medicine*** suggests this microRNA-targeted therapy may offer a totally new approach to the treatment of hepatitis C virus (HCV). In the small proof-of-concept study, weekly injections of miravirsen decreased viral loads by five weeks; 14 weeks after the injections stopped, 5 of 36 patients had undetectable levels of virus.

- **SHIRE** is buying **SARcode Bioscience**, which is developing lifitegrast for dry eye disease.

- **UNITED THERAPEUTICS' treprostinil diolamine** – For a second time, the FDA rejected this oral formulation to treat pulmonary arterial hypertension (PAH), issuing a complete response letter. The issue the first time was effectiveness. The company didn't say what the issue is this time.

- **ZIOPHARM ONCOLOGY's palifosfamide (ZIO-201)** – The company said it is ending development of this investigational agent for soft tissue sarcoma after the drug missed the primary endpoint in a Phase III trial.

REGULATORY NEWS

Anti-epileptics warnings not getting to neurologists

A survey of American Academy of Neurology members found that ~20% of healthcare professionals were not aware of major electronically reported FDA drug safety warnings for anti-epileptic medicines, such as valproate. Of those aware of the alerts, only 23% remembered the specific risk.

FDA under more pressure to better regulate opioids

The head of the Drug Enforcement Administration's Office of Diversion Control, Joseph Rannazzisi, sent a letter to the FDA urging the Agency to impose tougher rules on the way pharmaceutical companies market opioids – particularly **Purdue Pharma's OxyContin** (oxycodone) and **AbbVie's Vicodin** (hydrocodone + acetaminophen) – to physicians.

Rannazzisi supported a Citizen Petition submitted to the FDA in July 2012 by Physicians for Responsible Opioid Prescribing (PROP) and which was the subject of a two-day FDA public hearing in February 2013.

The petition asks the FDA to do three things:

1. Strike the term "moderate" from the indication for non-cancer pain.
2. Add a maximum daily dose equivalent to 100 milligrams of morphine for non-cancer pain.
3. Add a maximum duration of 90 days for continuous (daily) use for non-cancer pain.

In addition, Sen. Charles Schumer (D-NY) urged the FDA to require tamper-resistant formulations of generic OxyContin.

GAO: Federal oversight of bioterror labs inadequate

The Government Accountability Office (GAO) issued a report that found federal oversight of high-containment laboratories where dangerous microbes are studied is deficient, putting people, animals, and the food supply at risk from biological agents that could escape from the facilities.

Office of Inspector General issues fraud alert on PODs

The Office of the Inspector General (OIG) issued a special fraud alert on physician-owned distributorships (PODs). These are physician-owned entities that derive revenue from selling, or arranging for the sale of, implantable medical devices ordered by their physician-owners for use in procedures the physician-owners perform on their own patients at hospitals or ambulatory surgical centers (ASCs).

Apparently, the OIG does not like this business model, writing, "We believe that PODs are inherently suspect under the anti-kickback statute." The OIG is expected to issue a detailed POD report later this year. *Announcements like this generally preface investigations and charges of Medicare fraud under the anti-kickback statutes. Look for some high-profile cases to come.*

For more details, see:
https://oig.hhs.gov/fraud/docs/alertsandbulletins/2013/POD_Special_Fraud_Alert.pdf

FDA approvals/clearances

- **BIOGEN IDEC's Tecfidera (dimethyl fumarate, BG-12)** was approved to treat relapsing-remitting multiple sclerosis. The FDA is requiring that a patient's white blood cell count be measured before starting treatment and annually thereafter. There is no mandatory risk evaluation and mitigation strategy (REMS).
- **CANGENE's Botulism Antitoxin Heptavalent**, a botulism antitoxin, was approved to treat patients with documented or suspected exposure from a terrorist attack. It has orphan drug status.
- **JOHNSON & JOHNSON's Invokana (canagliflozin)** was approved, making it the first SGLT2 inhibitor for Type 2 diabetes. The FDA required five postmarketing studies:
  - A cardiovascular outcomes trial
  - An enhanced pharmacovigilance program to monitor for malignancies, serious cases of pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, liver abnormalities, and adverse pregnancy outcomes
  - A bone safety study
  - Two pediatric studies

FDA recalls/warnings

- **FISIOLINE's Lumix 2 and Lumix 3** – The company received a warning letter that the plant that makes these medical lasers is in violation of current Good Manufacturing Practice (cGMP) requirements.
- **HOSPIRA's 0.9% sodium chloride injection, UPS 1000 mL** – The company initiated a voluntary nationwide recall due to a confirmed customer report of brass particulate.
- **INSTRATEK**, which makes orthopedic implant systems and instruments, received a warning letter for cGMP violations and for the company's failure to adequately respond to the violations.
- **JOHNSON & JOHNSON's OneTouch Verio IQ** – The company recalled all of these blood glucose meters in the U.S. because the meters turn off instead of sounding a warning when glucose levels rise too high.
- **PALLIMED SOLUTIONS**, a Massachusetts compounding pharmacy, was ordered to stop producing drugs that were supposed to be made using sterile processes and to quarantine those in its possession. The company also recalled all such drugs that it had distributed since January 1, 2013. The recalled products include drugs for eye conditions, but, surprise, this does ***not*** include **Roche/Genentech's Avastin** (bevacizumab). Pallimed said the recall was precautionary and that it had not received any reports of any illnesses or injuries. Non-sterile compounding continues.
- **SPACELABS' BleaseSirius and BleaseFocus Anesthesia Workstations and Service Kits** – A Class I recall was initiated because of a defect in the CAS I/II absorbers that could lead to an increase in carbon dioxide concentration within the inhaled gas delivered to the patient, causing serious adverse health consequences, including death.

European regulatory news

- **BIOGEN IDEC's Tecfidera (dimethyl fumarate, BG-12)** – The European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) recommended approval of this oral multiple sclerosis drug.
- **BIOTRONIK's Iforia line** – These MRI-safe implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy defibrillators (CRT-D) received a CE Mark.
- **GILEAD SCIENCES' Stribild (emtricitabine + cobicistat + elvitegravir + tenofovir disoproxil)** – CHMP recommended approval of this combination HIV drug.

- **iTRAUMACAR's iTClamp Hemorrhage Control System**, a bleeding control device, received a CE Mark.
- **JOHNSON & JOHNSON and BAYER's Xarelto (rivaroxaban)** – CHMP said this antiplatelet drug should be approved as a preventive agent for patients with acute coronary syndrome (ACS).
- **OTSUKA's Pletal/Ekistol (cilostazol)** – The EMA recommended restricted use of medicines containing cilostazol due to concerns about side effects.
- **PFIZER's Bosulif (bosutinib)** – The European Commission granted conditional marketing authorization for this drug to treat chronic phase, accelerated phase, and blast phase Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML) in patients previously treated with one or more tyrosine kinase inhibitors (TKIs) who can't take **Novartis' Gleevec** (imatinib) or **Tasigna** (nilotinib) or **Bristol-Myers Squibb's Sprycel** (dasatinib).

Regulatory news from other countries

- ***Canada:*** Starting on June 1, 2013, Health Canada will require all regulatory submissions by pharmaceutical companies to be done electronically.
- ***Egypt:*** In an effort to streamline device approvals, the Central Administration of Pharmaceutical Affairs issued revisions to its registration standards that include increasing the list of reference countries accepted by the agency and expediting some registration deadlines.
- ***Japan:***
  - **PFIZER's Xeljanz (tofacitinib)** – This oral JAK inhibitor was approved to treat rheumatoid arthritis and initially will be available at institutions participating in a patient monitoring program.
  - **ROCHE/CHUGAI's Actemra (tocilizumab)** – A subcutaneous formulation of this rheumatoid arthritis drug, an anti-IL-6, was approved by the Japanese Ministry of Health, Labour, and Welfare to treat patients who do not respond to ≥1 existing therapy.

2013 FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
April 8	**Bausch & Lomb's Trulign Toric** implantable intraocular lens for post-cataract surgery patients	FDA's Ophthalmic Devices Advisory Committee
April 11	Potential effects of extreme weather and natural disasters on **medical device safety and quality**	FDA's Device Good Manufacturing Practice Advisory Committee
April 15	**MAP Pharmaceuticals' Levadex** (dihydroergotamine), inhaled migraine drug	PDUFA date
April 25	Reclassification of **methotrexate enzyme immunoassays, phencyclidine (PCP) enzyme immunoassays, and PCP radioimmunoassays**	FDA's Clinical Chemistry and Clinical Toxicology Devices Advisory Committee
April 26	Reclassification of **isoniazid test strips**	FDA's Clinical Chemistry and Clinical Toxicology Devices Advisory Committee
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 Procysbi** (cysteamine bitartrate delayed-release, RP-103) to treat nephropathic cystinosis	PDUFA date (extended from January 30, 2013)
April 30	**Titan Pharmaceuticals' Probuphine** (buprenorphine implant) for opioid dependence	PDUFA date
May 2	**Allergan's Juvéderm Voluma XC**, a facial filler with hyaluronic acid and lidocaine	FDA's General and Plastic Surgery Devices Advisory Committee
May 2	**Aveo and Astellas' Tivopath** (tivozanib) for advanced renal cell carcinoma	FDA's Oncologic Drugs Advisory Committee
May 12	**GlaxoSmithKline** and **Theravance's Breo/Relvar** (fluticasone furoate + vilanterol) to treat chronic obstructive pulmonary disease (COPD)	PDUFA date
May 31	**Depomed's Sefelsa** (gabapentin extended-release), a hot-flash treatment (formerly known as Serada)	PDUFA date
June 20	**Dainippon Sumitomo Pharma/Sunovion Pharmaceuticals' Latuda** (lurasidone), a schizophrenia drug for use in treating bipolar disorder	PDUFA date
June 28	**Hisamitsu Pharmaceutical/Noven Pharmaceuticals' Pexeva** (paroxetine mesylate), a low-dose SSRI antidepressant to treat non-hormonal hot flashes in menopausal women	PDUFA date
July tba	**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
August 17	**ViiV Healthcare's dolutegravir** for HIV	PDUFA date
September tba	**Sanofi/Genzyme's Lemtrada** (alemtuzumab) for multiple sclerosis	PDUFA date
October 2	**Lundbeck** and **Takeda's Brintellix** (vortioxetine), an antidepressant for major depressive disorder	PDUFA date
October 3	**Pfizer** and **Ligand Pharmaceuticals' Aprela** (bazedoxifene/conjugated estrogens) to treat menopausal symptoms and osteoporosis prevention	PDUFA date
October 19	**Actelion's Opsumit** (macitentan), a dual endothelin receptor antagonist to treat pulmonary arterial hypertension	PDUFA date
October 21	**AMAG Pharmaceuticals' Feraheme** (ferumoxytol) expanded indication	PDUFA date
October 28	**Neos Therapeutics' NT-0202** (extended-release tablet formulation of amphetamine polistirex) to treat ADHD	PDUFA date
December 18	**GlaxoSmithKline** and **Theravance's Anoro** (umeclidinium bromide + vilanterol) for COPD	PDUFA date