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 coverage of the **International Myeloma Workshop** in Kyoto, Japan.

SHORT TAKES

- **ASTRAZENECA's fostamatinib** missed one of the two primary endpoints in the Phase III OSKIRA-1 trial in rheumatoid arthritis. The antibody met the ACR20 goal but failed to improve the modified Total Sharp Score.

- **BIOGEN IDEC's Tecfidera (dimethyl fumarate, BG-12)** – The company priced this oral multiple sclerosis drug at $54,900 a year, which is about 8.5% less than **Novartis' Gilenya** (fingolimod).

- **BRISTOL-MYERS SQUIBB's Yervoy (ipilimumab) and ROCHE/GENENTECH's Zelboraf (vemurafenib)** – A Phase I trial in melanoma that combined these two targeted agents (an immunotherapy and a BRAF inhibitor) was halted after four of the first six patients in one cohort (960 mg BID) and two of the first four patients in a second, lower-dose cohort (720 mg BID) developed Grade 2/3 ALT elevations. One patient in each cohort also had Grade 2/3 elevations of bilirubin. The hepatotoxicity resolved with temporary discontinuation of the drugs or use of glucocorticoids.

- **ENLIVEX THERAPEUTICS' Apocell**, an investigational drug to treat graft-versus-host disease (GVHD), was granted orphan drug status by the FDA.

- **Influenza** – Twenty-one people have contracted H7N9 avian flu in China, and six of them died. This reportedly is the first time avian H7N9 flu has infected humans, and the victims apparently have not had any contact with each other, and most have had no contact with birds or poultry. However, it does not appear that the virus is being transmitted from person to person. As a precaution, the Centers for Disease Control and Prevention (CDC) is already working on a seed vaccine against H7N9.

- **LILLY's Cymbalta (duloxetine)** – A 231-patient Phase III study published in the ***Journal of the American Medical Association*** found that this antidepressant may reduce neuropathic pain associated with some chemotherapies. Over five weeks, Cymbalta patients had significantly bigger decreases in pain than placebo (1.06 vs. 0.34 on the BPI-SF, p=0.003). In addition, 59% of Cymbalta patients vs. 38% of placebo patients reported a pain decrease of any amount. The data were presented at ASCO 2012.

- **LONZA** reportedly is re-evaluating whether it should go ahead with the planned biosimilar partnership with **Teva**, given the cost and regulatory uncertainty in developing biosimilars.

- **MERRIMACK PHARMACEUTICALS' MM-121** missed the primary endpoint in one 50-patient cohort of a Phase II trial in non-small cell lung cancer that had progressed on an anti-EGFR inhibitor. MM-121 + **Roche/Genentech's Tarceva** (erlotinib) did not extend progression-free survival by the 40% goal at four months.

- **NAVIDEA BIOPHARMACEUTICALS' Lymphoseek (technetium 99m tilmanocept)** – The company said this oncology imaging agent met the primary endpoint in a Phase III trial, correctly identifying the first lymph node reached by the disease in 38 of 39 head and neck cancer patients. The false-negative rate was 2.56%. Navidea plans to submit Lymphoseek to the FDA for expanded approval later this year.

- **NOVAVAX's respiratory syncytial virus (RSV) vaccine** met the primary endpoint in a Phase II trial, inducing a potentially protective immune response in an infant through an antibody transfer from the mother.

- **PFIZER** signed a deal with **Bind Therapeutics** (formerly Bind Biosciences) under which the two companies will work together on nanomedicines, using Bind's "medicinal nano-engineering" platform.

NEWS IN BRIEF

HOLOGIC's Selenia – users appear happy

A survey (not commissioned by Hologic) by KLAS Research, an independent healthcare research firm, of Hologic 3D mammography sites found:

- Tomosynthesis is detecting cancers that would not previously have been detected with traditional digital mammography.
- Nearly 90% said they are achieving a positive return on investment with the technology.
- Users reported a significant decrease in false-positive callbacks, an increase in new patients, and workflow improvements.

Hospital-employed physicians – on the increase

A survey by Jackson Healthcare found that 44% of responding hospitals completed acquisitions of physician practices last year, and 52% plan to acquire physician practices this year. More than half (58%) said they are buying the practices for competitive reasons.

What types of practices do they plan to buy next? Among respondents, 54% plan to acquire family practice physician offices, and 26% are looking at internal medicine practices. Interestingly, 70% of hospital executives said physicians are actually approaching them about buying their practices.

Lung cancer – new testing guidelines

The International Association for the Study of Lung Cancer (IASLC), the College of American Pathologists (CAP), and the Association for Molecular Pathology (AMP) jointly issued new guidelines – published in the ***Archives of Pathology & Laboratory Medicine* (*APLM*)**, the ***Journal of Thoracic Oncology***, and ***The Journal of Molecular Diagnostics*** – that set standards for EGFR and ALK testing of lung cancer patients.

The key recommendation was that all patients with advanced lung adenocarcinoma should be tested for EGFR and ALK abnormalities, regardless of smoking history, gender, or ethnicity.

MEDICINOVA's ibudilast (MN-166) – moving ahead

The FDA granted fast track status to this investigational treatment for methamphetamine addiction. Phase I results suggest it might reduce drug craving and improve cognitive functioning. A 140-patient Phase II study, funded by the National Institute on Drug Abuse (NIDA), is planned to start in mid-2013 testing ibudilast BID vs. placebo. Ibudilast has been approved in Japan for more than 20 years to treat asthma and post-stroke complications, and it was licensed to MediciNova in 2004 as a potential treatment for multiple sclerosis before the meth use was discovered.

MERCK

- **V710.** In a >7,000-patient study published in the ***Journal of the American Medical Association***, this vaccine failed to prevent *Staphylococcus aureus* infections in patients undergoing cardiothoracic surgery any better than placebo. By 90 days, staph infections had occurred in 0.624% (22 of 3,528) of vaccinated patients vs. 0.728% (27 of 3,517) of placebo patients. Multi-organ failure occurred in 31 vaccinated patients vs. 17 control patients, and all five deaths in the study due to multi-organ failure were in vaccinated patients.
- **Suvorexant (MK-4305).** An animal study (in rats and monkeys) published in ***Science Translational Medicine*** found that this investigational insomnia drug, a dual orexin receptor antagonist (DORA), is effective without causing memory loss and attention problems that occur with current medications.

Orthopedic pricing – wide variance

A study presented at the American Academy of Orthopaedic Surgeons meeting by researchers at the University of California, Irvine, found wide differences in the price hospitals paid for orthopedic devices, including:

- The mean price of a pedicle screw was $878, but the price ranged from as little as $400 to as much as $1,843.
- The mean price of an anterior cervical plate was $1,068, ranging from $540-$2,388.
- The mean price of an interbody case was $2,975, ranging from $938-$7,200.

Prostate cancer – continuous ADT better than intermittent

A study funded by the National Cancer Institute (NCI) and others – published in the ***New England Journal of Medicine*** – found intermittent androgen deprivation therapy (ADT) is not better than continuous ADT for prostate cancer patient survival. Average survival was 5.8 years with continuous therapy vs. 5.1 years with intermittent therapy. Patients on intermittent therapy did have better erectile function and mental health – but only for the first three months of therapy.

Statins – if at first you don't succeed, try again

A study published in the ***Annals of Internal Medicine*** found that some patients who stop using statins due to adverse events can successfully take them again by starting at a lower dose. The researchers analyzed data over nine years on 107,835 statin patients at Brigham and Women's Hospital and Massachusetts General Hospital. Of the 11,124 who discontinued because of a side effect, half started again at a lower dose or with a different statin, and 90% of those restarts remained on the second-try statin for 12 months or more.

The researchers concluded: "If someone has to go off of a statin due to side effects like muscle aches, it may be worth trying the drug again, especially if a person has had a previous heart attack or stroke or has established heart disease."

VERTEX PHARMACEUTICALS' VX-135 and BRISTOL-MYERS SQUIBB's daclatasvir – an engagement more than a marriage

In a non-exclusive agreement, the two companies will collaborate in Phase II studies of an all-oral, once-daily regimen of VX-135 (an NS5B polymerase inhibitor licensed from **Alios BioPharma**) + daclatasvir (an NS5A nucleotide inhibitor) in hepatitis C virus (HCV) patients. Both studies will be run by Vertex.

a. A study in 20 treatment-naïve HCV-1 patients to start in 2Q13.

b. A 250-patient study in HCV-1-2-3 patients, including cirrhotics, to start in 2H13.

Vertex will also conduct co-formulation activities to evaluate the potential for development of a once-daily fixed-dose combination regimen. What happens after Phase II is not part of the agreement.

REGULATORY NEWS

FDA and opioids

In an FDA blog, FDA Commissioner Margaret Hamburg, MD, talked about the FDA's "comprehensive approach" to the opioid problem without announcing any new or tougher steps. She said the FDA is:

- Encouraging basic research in pain.
- Facilitating and incentivizing the development of abuse-deterrent formulations.
- Modifying opioid labeling for safety, accuracy, and clarity. She said the FDA has made "many changes to opioid medication labels…and today they contain some of the most restrictive language that can be found in a drug label." She also made an oblique reference to a Citizen Petition filed in July 2012 by Physicians for Responsible Opioid Prescribing (PROP), asking the FDA for three changes to the labels on opioids – a limit on duration, a maximum daily dose, and a restriction on use for severe pain – saying, "If additional improvements could make the labels more effective, it's important we explore them as part of our overall efforts to improve the safety of opioids…We're currently considering potential changes."
- Encouraging greater prescriber education and patient education.
- Supporting – and hoping for legislation that mandates – training of prescribers before they register with the Drug Enforcement Agency and receive their license to prescribe a controlled substance.
- Addressing innovative ways to package and store opioids to prevent diversion.
- Improving the availability of products that treat abuse and overdose, "We know there is widespread interest in exploring the broader uses of [naloxone] and are currently

encouraging new technology such as intranasal or auto-injector formulations that would be easier to use in non-medical settings such as the home."

FDA approvals/clearances

- **CHROMAGEN VISION's ChromaGen lenses** were cleared for improving reading speed and accuracy as well as handwriting in patients with dyslexia and related conditions.
- **CRYOLIFE's Hemodialysis Reliable Outflow (HeRO) system**, a next-generation hemodialysis access graft, received 510(k) clearance.
- **INVIVO THERAPEUTICS** received humanitarian use device classification for its bioscaffold for treating spinal cord injuries.
- **LENSAR's LensAR Laser System** received expanded clearance for use of this cataract surgery laser device for the execution of arcuate incisions during cataract surgery as well as the corneal incisions that were already cleared.
- **MEDTRONIC's Affinity Fusion**, a blood oxygenation device, received 510(k) clearance.
- **TEVA's Quartette (levonorgestrel/ethinyl estradiol and ethinyl estradiol)**, a next-generation, extended-regimen oral contraceptive, was approved.

FDA recalls/warnings

- **BIOTEST PHARMACEUTICALS' Bivigam (immune globulin intravenous, human)** – One lot of 100 mL vials was recalled because visible particles were observed in some vials.
- **JOHNSON & JOHNSON/ANIMAS' 2020 Insulin Infusion Pump** – A Class I recall was initiated because a component issue may trigger the pumps to sound a false alarm or warning. The device also has a software limitation that will make it stop working on December 31, 2015. Users are advised to ask the company for a free replacement device.

European regulatory news

- **APOLLO ENDOSURGERY's OverStitch Endoscopic Suturing System** received a CE Mark.
- **APTUS ENDOSYSTEMS' HeliFX System** – This thoracic-length abdominal aortic aneurysm system received a CE Mark.
- **BIOMARIN PHARMACEUTICAL's BMN-190** – The company applied to the U.K.'s Medicines and Healthcare products Regulatory Agency for approval to initiate a Phase I/II trial of this investigational drug to treat neuronal ceroid lipofuscinosis type 2, a form of Batten disease, and hopes to start enrollment later this year.
- **MEDTRONIC's Sentrant Introducer Sheath**, for use with the company's abdominal aortic aneurysm devices accessed through the femoral artery, was granted a CE Mark.
- **TRUEVISION 3D SURGICAL's Refractive Cataract Toolset**, computer-guided 3D software for astigmatic correction and intraocular lens (IOL) alignment during cataract surgery, received a CE Mark. It already had FDA clearance.

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

This is NICE's new name. "Care" replaced "Clinical" to reflect an expanded role in social care, but it will still be called NICE.

Regulatory news from other countries

- ***China:*** **SANOFI** plans to open four new production facilities in China this year.
- ***Vietnam:*** **SANOFI** is expanding its presence in Southeast Asia, investing $75 million in a new manufacturing plant in Vietnam that is expected to be operational by 2016.

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 22	Discussion of strategies and objectives for a **global consortium of cardiovascular medical device registries**, starting with TAVR	FDA public workshop
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	Discussion of general factors in **risk communication about FDA-regulated products**, including messaging in the context of competing communicators	FDA's Risk Communication 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	Discussion of how to communicate effectively about the FDA's **adverse event reporting system** (AERS)	FDA's Risk Communication Advisory Committee
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